UNIVERSIDAD COMPLUTENSE DE MADRID
FACULTAD DE CIENICAS QUÍMICAS
Departamento de Química Orgánica I

TESIS DOCTORAL

Nuevos métodos catalíticos de ciclación/transposición de alenos basados en metales de transición

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

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TESIS DOCTORAL

SARA CEMBELLÍN SANTOS

Madrid, 2016

A mis padres
y mi hermana

“La vida no es fácil para ninguno de nosotros. Pero, ¿qué importa? Hay que perseverar y, sobre todo, tener confianza en uno mismo. Hay que sentirse dotado para realizar cualquier cosa y alcanzarla cueste lo que cueste.”

(Marie Curie)

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D. Benito Alcaide Alañón, Catedrático de Química Orgánica de la Facultad de Ciencias Químicas de la Universidad Complutense de Madrid, **D. Pedro Almendros Requena**, Profesor de Investigación del Instituto de Química Orgánica General del Consejo Superior de Investigaciones Científicas, y **Dña. Teresa Martínez del Campo**, Profesora Contratada Doctor de Química Orgánica de la Facultad de Ciencias Químicas de la Universidad Complutense de Madrid

CERTIFICAN:

Que la presente Memoria, titulada **NUEVOS MÉTODOS CATALÍTICOS DE CICLACIÓN/TRANSPOSICIÓN DE ALENOS BASADOS EN METALES DE TRANSICIÓN**, ha sido realizada bajo su dirección en el grupo de **Lactamas y Heterociclos Bioactivos** (Unidad Asociada al CSIC) del Departamento de Química Orgánica I de la Universidad Complutense de Madrid, por la Licenciada en Química Dña. **Sara Cembellín Santos**, y autorizan su presentación para ser calificada como Tesis Doctoral.

Madrid, 21 de Octubre de 2016

Fdo. Prof. Benito Alcaide, Prof. Pedro Almendros y Dra. Teresa Martínez

Parte de los resultados obtenidos durante la elaboración de esta Memoria han dado lugar a las siguientes publicaciones:

1. Alcaide, B.; Almendros, P.; Cembellín, S.; Martínez del Campo, T.; Fernández, I.
   "Gold-catalysed tuning of reactivity in allenes: 9-*endo* hydroarylation versus formal 5-*exo* hydroalkylation"
   Chem. Commun. **2013**, *49*, 1282-1284.

2. Alcaide, B.; Almendros, P.; Alonso, J. M.; Cembellín, S.; Fernández, I.; Martínez del Campo, T.; Torres, M. R.
   "Iodine recycling via 1,3-migration in iodoindoles under metal catalysis"
   Chem. Commun. **2013**, *49*, 7779-7781.

3. Alcaide, B.; Almendros, P.; Cembellín, S.; Martínez del Campo, T.
   "Acid-Catalyzed Synthesis of α,β-Disubstituted Conjugated Enones by a Meyer–Schuster-Type Rearrangement in Allenols"
   Adv. Synth. Catal. **2015**, *357*, 1070-1078.

4. Alcaide, B.; Almendros, P.; Cembellín, S.; Martínez del Campo, T.
   "Gold as Catalyst for the Hydroarylation and Domino Hydroarylation/N1−C4 Cleavage of β-Lactam-Tethered Allenyl Indoles"
   J. Org. Chem. **2015**, *80*, 4650-4660.

5. Alcaide, B.; Almendros, P.; Cembellín, S.; Martínez del Campo, T.; Muñoz, A.
   "Iron-catalyzed domino indole fluorination/allenic aza-Claisen"
   Chem. Commun. **2016**, *52*, 6813-6816.

6. Alcaide, B.; Almendros, P.; Cembellín, S.; Fernández, I.; Martínez del Campo, T.
“Metal-Catalyzed Cyclization Reactions of 2,3,4-Trien-1-ols: A Joint Experimental–Computational Study”
Chem. Eur. J. **2016**, *22*, 11667-11676.

7. Alcaide, B.; Almendros, P.; Cembellín, S.; Fernández, I.; Martínez del Campo, T.
“Stereoselective Synthesis of Strained Cage Compounds *via* Gold-Catalyzed Allene Functionalization”
Chem. Commun. **2016**, *52*, 10265-10268.

Abreviaturas utilizadas en esta Memoria

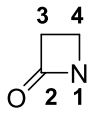
En la presente Tesis Doctoral se han utilizado las abreviaturas y acrónimos recomendados en *"Guidelines for Authors" (J. Org. Chem*. Updated versión January 2016) y las indicadas a continuación:

AMCPB	ácido *m*-cloroperbenzoico
ATCC	American Type Culture Collection
Bpin	bis(pinacolato)diboro
BQ	benzoquinona
CFS	fluoroxisulfato de cesio
col.	colaboradores
dba	dibencilidenoacetona
$(DHQ)_2PHAL$	hidroquinina 1,4-ftalacinedil-dieter
dig	digonal
dppb	1,3-bis(difenilfosfino)butano
dppe	1,2-bis(difenilfosfino)etano
dppf	1,2-bis(difenilfosfino)ferroceno
dppm	1,3-bis(difenilfosfino)metano
EDG	Electron Donating Group (grupo dador de electrones)
e.e.	exceso enantiomérico
EWG	Electron Withdrawing Group (grupo aceptor de electrones)
HBTU	*N,N,N',N'*-tetrametil-*O*-(1*H*-benzotriazol-1-yl)uronio hexafluorofosfato
IC50	half maximal inhibitory concentration (concentración inhibitoria para obtener un 50% del efecto máximo)
INT	intermedio
IPr	1,3-bis(2,6-diisopropilfenil)imidazol-2-ilideno
Kcal	kilocaloría
NFSI	*N*-fluorobencenosulfonimida

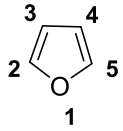
PBrB	*p*-bromobencilo
PCM	Polarizable Continuum Model
PFP	*p*-fluorofenilo
PMP	*p*-metoxifenilo
r.d.	relación de diastereómeros
Rto.	rendimiento
SPPS	Solid phase peptide synthesis (síntesis de péptidos en fase sólida)
t.a.	temperatura ambiente
TBACN	cianuro de tetrabutilamonio
TBAI	yoduro de tetrabutilamonio
TBS	*terc*-butildimetilsililo
TBDPS	*terc*-butildifenilsililo
TDMPP	tris(2,6-dimetoxifenil) fosfina
trig	trigonal
TSMT	2-(trimetilsili)tiazol
XRD	X-Ray Diffraction (difracción de rayos X)

Nomenclatura y numeración utilizada en esta Memoria

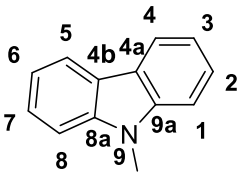
La numeración y nomenclatura utilizada en esta Memoria para los compuestos sintetizados en la presente Tesis Doctoral es la que se indica a continuación:



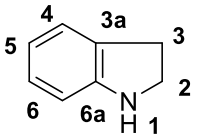
β-lactama
(2-azetidinona)



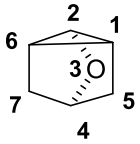
furano



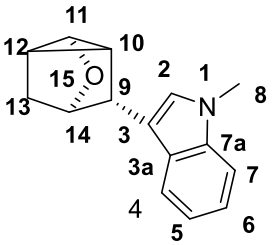
carbazol



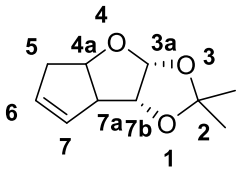
indolina



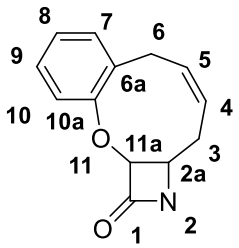
3-oxatriciclo
[2.2.1.0^{2,6}]heptano



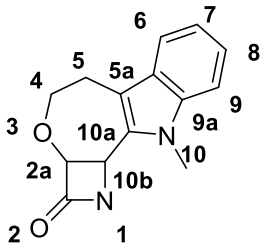
1-metil-3-(3-oxatriciclo
[2.2.1.0^{2,6}]heptan-5-il)-1*H*-indol



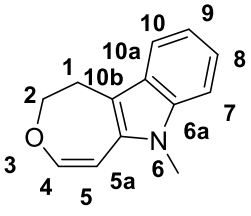
2,2-dimetil-3a,4a,7a,7b-
tetrahidro-5*H*-ciclopenta[4,5]
furo[2,3-*d*][1,3]dioxol



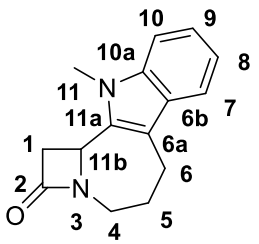
2a,3,6,11a-tetrahidro-
1*H*-2λ^2-benzo[8,9]oxonino
[3,2-*b*]azet-1-ona



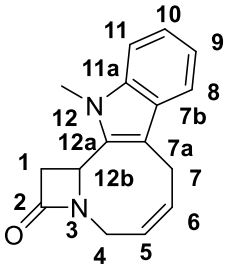
10-metil-4,5,10,10b-tetrahidro-1λ^2-
azeto[3',2':2,3]oxepino[4,5-*b*]indol-
2(2a*H*)-ona



6-metil-1,6-dihidro-
2*H*-oxepino[4,5-*b*]indol



11-metil-1,4,5,6,11,11b-hexahidro-
2*H*-azeto[1',2':1,2]azepino
[3,4-*b*]indol-2-ona



12-metil-4,7,12,12b
-tetrahidroazeto[1',2':1,2]azocino
[3,4-*b*]indol-2(1*H*)-ona

ÍNDICE

I. INTRODUCCIÓN

I. INTRODUCCIÓN

En los últimos 20 años la química de alenos se ha estudiado ampliamente debido a la interesante reactividad que presentan. Los alenos han pasado de ser una mera curiosidad de laboratorio a convertirse en excelentes candidatos para la preparación de una gran variedad de compuestos de alto interés químico y biológico.[1] En especial, las reacciones de alenos catalizadas por metales de transición han experimentado un notable desarrollo.[2]

Sus análogos superiores, los cumulenos, han despertado un gran interés en los últimos años debido a sus potenciales aplicaciones en el diseño de fármacos antitumorales,[3] así como a sus importantes propiedades eléctricas y fotofísicas.[4] Además, los cumulenos representan intermedios sintéticos muy versátiles en Síntesis Orgánica.[5]

Por otro lado, de entre la enorme variedad de estructuras heterocíclicas, aquellas que contienen un núcleo β-lactámico y/o indólico son particularmente relevantes debido a su presencia en productos naturales y sintéticos con actividad biológica, tales como antibióticos, aminoácidos, hormonas o fármacos.[6]

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1 Para publicaciones recientes véanse: a) Guo, H.; Kreuzenbeck, N. B.; Otani, S.; Garcia-Altares, M.; Dahse, H.–M.; Weigel, C.; Aanen, D. K.; Hertweck, C.; Poulsen, M.; Beemelmanns, C. *Org. Lett.* **2016**, *18*, 3338. b) Cai, L.; Zhang, K.; Kwon, O. *J. Am. Chem. Soc.* **2016**, *138*, 3298. c) Shen, X.–Y.; Peng, X.–S.; Wong, H. N. C. *Org. Lett.* **2016**, *18*, 1032. d) Yu, Q.; Ma, S. *Eur. J. Org. Chem*. **2015**,1596. e) Bates, R. W.; Lim, C. J.; Collier, S. J.; Sukumaran, J. *Asian J. Org. Chem.* **2015**, *4*, 652. f) Sears, J. E.; Barker, T. J.; Boger, D. L. *Org. Lett.* **2015**, *17*, 5460.

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6 Para la relevancia de β-lactamas véanse: a) Veinberg, G.; Vorona, M.; Shestakova, I.; Kanepe, I.; Lukevics, E. *Curr. Med. Chem.* **2003**, *10*, 1741. b) Southgate, R.; Branch, C.; Coulton, S.; Hunt, E. *Curr. Org. Chem.* **2002**, *6*, 245. Para la relevancia de indoles véanse: c) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. d) Sundberg, R. J. *Indoles*; Academic Press: New York, 1996.

El interés del esqueleto β-lactámico no se limita únicamente a su actividad farmacológica. Su elevada tensión anular hace de este núcleo un intermedio sintético muy versátil y de gran aplicabilidad en Síntesis Orgánica, dando lugar al desarrollo de nuevas metodologías sintéticas basadas en el sintón β-lactámico.[7]

Por otra parte, la desaromatización de indoles ha ganado especial importancia en Síntesis Orgánica a causa de la alta bioactividad que presentan las indolinas resultantes.[8] En particular, aquellas que contienen al menos un átomo de flúor en su estructura son de gran relevancia ya que presentan una importante actividad biológica gracias a su alta lipofilia y estabilidad metabólica.[9] Por ello, en los últimos años se han descrito un gran número de métodos de fluoración de indoles funcionalizados, que permiten obtener de manera directa una gran variedad de indolinas fluoradas.[10]

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8 a) Denizot, N.; Tomakinian, T.; Beaud, R.; Kouklovsky, C.; Vincent, G. *Tetrahedron Lett.* **2015**, *56*, 4413. b) Ding, Q.; Zhou, X.; Fan, R.; *Org. Biomol. Chem.* **2014**, *12*, 4807. c) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447.

9 a) Gouverneur, V.; Muller, K. *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications;* Imperial College Press: London, 2012.

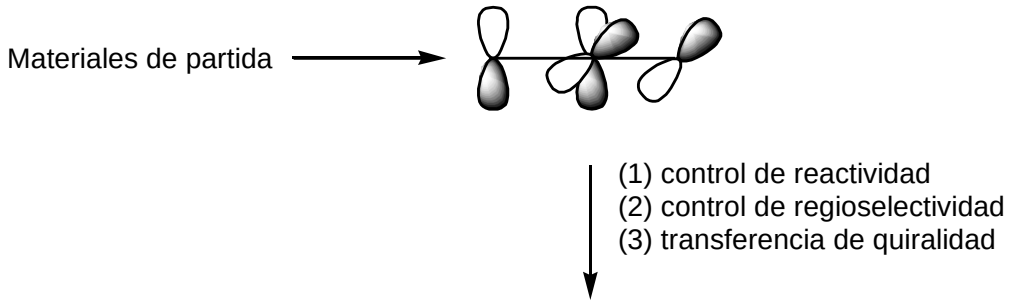
10 a) Fong, J. Z. M.; Choo, S. S. S.; Richard, J.–A.; Garland, M. V.; Guo, L.; Johannes, C. W.; Nguyen, T. M. *Eur. J. Org. Chem*. **2015**, 995. b) Wang, T.; Hoon, D. L.; Lu, Y. *Chem. Commun.* **2015**, *51*, 10186. c) Lozano, O.; Blessley, G.; Martínez, del Campo, T.; Thompson, A. L.; Giuffredi, G. T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. *Angew. Chem. Int. Ed*. **2011**, *50*, 8105.

II. ANTECEDENTES GENERALES

II. ANTECEDENTES GENERALES

II.1. Reacciones de alenos catalizadas por metales de transición

La síntesis del primer aleno data del año 1887,[11] pero su estructura no se confirmó hasta el año 1954.[12] Durante mucho tiempo se pensó que eran compuestos altamente inestables y por ese motivo, sus aplicaciones químicas y sintéticas no fueron bien establecidas. Sin embargo, la presencia de dos dobles enlaces acumulados en su estructura hacía a estos compuestos bastante interesantes.[13] Entre sus propiedades más importantes cabe destacar las siguientes: 1) debido a la posibilidad de albergar hasta cuatro sustituyentes en su estructura, los convierten en punto de partida de un gran número de rutas de síntesis, 2) la densidad electrónica así como la reactividad de cada átomo de carbono del aleno se puede modular en función del sustituyente, 3) la inherente quiralidad axial permite la síntesis estereoselectiva de alenos ópticamente activos, así como la transferencia de quiralidad desde el aleno al producto final (Esquema II.1).



Esquema II.1

11 Burton, B. S.; Pechman, H. V. *Chem. Ber*. **1887**, *20*, 145.

12 Jones, E. R. H.; Mansfield, G. H.; Whiting, M. C. *J. Chem. Soc*. **1954**, 3208.

13 a) *Allenes in Organic Synthesis*; Schuster, H. F.; Coppola, G. M., Eds. John Wiley & Sons: New York, 1984. b) *The Chemistry of Ketenes, Allenes and Relates Compounds Part 1*; Patai, S., Ed. John Wiley & Sons: New York, 1980.

Por todo ello, los alenos son precursores sintéticos muy útiles en Síntesis Orgánica debido a su versatilidad para llevar a cabo diferentes transformaciones.[14]

De entre los diferentes modos de reacción, aquel que implica la activación de uno de los dobles enlaces cumulénicos por tratamiento con un ácido de Lewis o Brönsted es especialmente útil ya que permite un ataque nucleófilo posterior que conlleva la formación de un nuevo enlace C–C o C–heteroátomo a través de una transformación inter- o intramolecular. Debido a la inherente quiralidad axial, la especie alénica permite la transferencia de la quiralidad al producto final, lo que supone un método atractivo en síntesis estereoselectivas.

La mayor parte de las reacciones de ciclación de alenos están catalizadas por metales y entre ellas, las que resultan de un ataque nucleófilo intramolecular han recibido mucha más atención que las correspondientes adiciones intermoleculares. El catalizador metálico puede coordinarse a cualquiera de los dos dobles enlaces del aleno, y la regioselectividad del subsiguiente ataque nucleófilo dependerá tanto de la estructura del sustrato, en particular de la longitud del fragmento existente entre el aleno y el nucleófilo, así como del catalizador metálico utilizado (Esquema II.2).

Tal y como se muestra en el Esquema II.2 se pueden obtener cuatro posibles productos de ciclación (dos *endo*- y dos *exo*-), pero la formación de los anillos de 5 o 6 miembros a través de las especies A o D que implican especies σ-metal por ataque nucleófilo al carbono próximo o terminal del aleno, están más favorecidos que los productos que provienen del ataque nucleófilo al carbono central del aleno (vía intermedios B y C).

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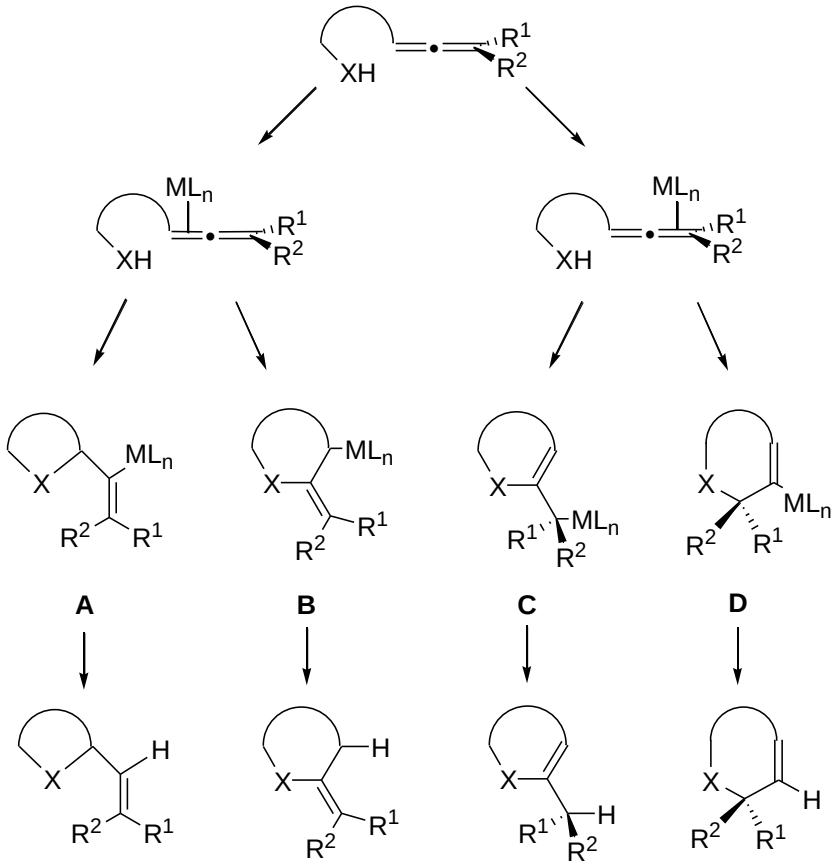
[14] Revisiones: a) Véase referencia 2. b) Lechel, T.; Pfrengle, F.; Reissig, H.–U.; Zimmer, R. *ChemCatChem* **2013**, *5*, 2100. c) Yu, S.; Ma, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 3074. d) Rivera-Fuentes, P.; Diederich, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 2818. e) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. f) Alcaide, B.; Almendros, P. *Adv. Synth. Catal.* **2011**, *353*, 2561. g) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Soc. Rev.* **2010**, *39*, 783. h) Brasholz, M.; Reissig, H.-U.; Zimmer, R. *Acc. Chem. Res.* **2009**, *42*, 45. i) Widenhoefer, R. A. *Chem. Eur. J.* **2008**, *14*, 5382. j) Bongers, N.; Krause, N. *Angew. Chem. Int. Ed.* **2008**, *120*, 2178. k) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555. l) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. m) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. n) *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004. o) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2004**, 3377. p) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701. q) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev*. **2002**, *31*, 12. r) Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2000**, *39*, 3590. s) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067.



Esquema II.2

Una vez enmarcado el contexto, se llevará a cabo una revisión bibliográfica de algunas de las reacciones más importantes de carbociclación y transposición de alenos catalizadas por metales.

II.1.1. Reacciones de carbociclación de alenos

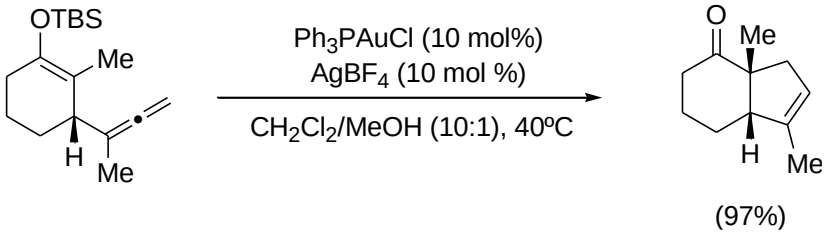
Son numerosos los ejemplos descritos en la literatura que implican adiciones de nucleófilos heteroatómicos (O, N, S) a alenos catalizadas por metales.[15] Sin embargo, son menos frecuentes las reacciones de adición de nucleófilos carbonados a alenos descritas hasta la fecha.

[15] Para revisiones recientes de química de alenos catalizada por metales, véanse: Pd: a) referencia 14b. b) Le Bras, J.; Muzart, J. *Chem. Soc. Rev.* **2014**, *43*, 3003. Au: c) referencia 14e. Ag y Pt: d) Muñoz, M. P. *Chem. Soc. Rev.* **2014**, *43*, 3164.

a) Reacciones de carbociclación catalizadas por oro

Los catalizadores de oro, por tratarse de ácidos suaves, y por su carácter carbofílico, son muy adecuados para la activación selectiva de alenos en presencia de otras funcionalidades reactivas.[16]

La primera reacción de carbociclación de alenos catalizada por oro data del año 2006. Toste y col. emplearon silil-enol-éteres alénicos para la creación de enlaces C–C a través de ciclaciones intramoleculares catalizadas por oro. Así, el tratamiento de éstos con un catalizador catiónico de oro condujo a la obtención de hexahidroindanonas a través de una ciclación 5-*endo* (Esquema II.3).[17] En estas transformaciones, se requiere agua o metanol como fuente externa de protones, necesarios para la protodesauración del intermedio vinil-oro. De forma análoga, Ma consiguió obtener ciclopentenos partiendo de β-cetoésteres alénicos.[18]



Esquema II.3

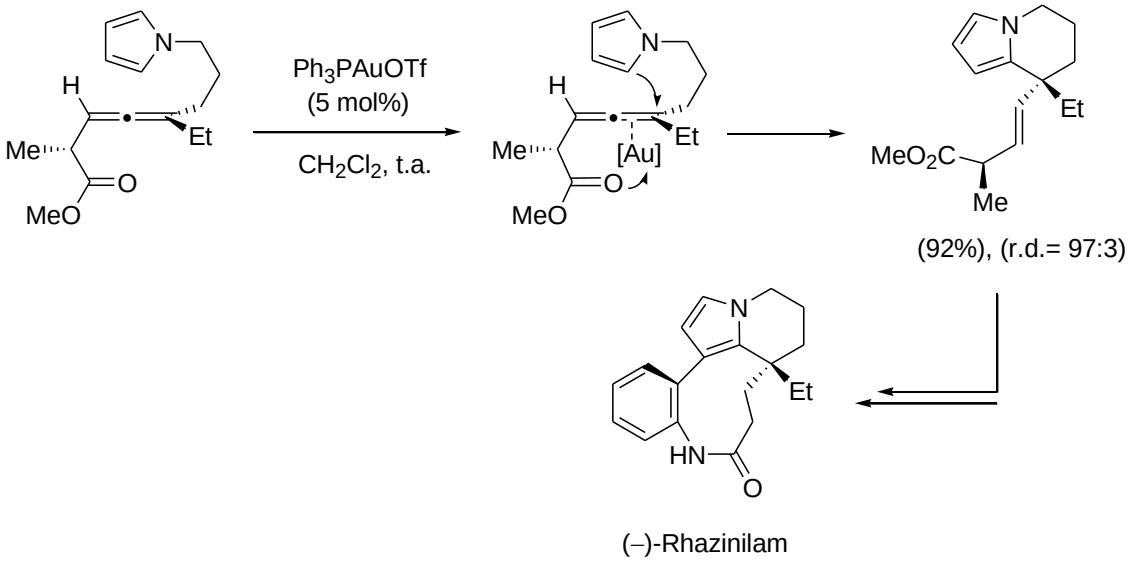
La mayoría de las reacciones de carbociclación intramolecular catalizadas por oro en alenos utilizan como nucleófilos anillos aromáticos o heteroaromáticos

16 a) Pflästerer, D.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2016**, *45*, 1331. b) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028. c) Jia, M.; Bandini, M. *ACS Catal.* **2015**, *5*, 1638. d) Hashmi, A. S. K. *Acc. Chem. Res.* **2014**, *47*, 864. e) Zhang, L. *Acc. Chem. Res.* **2014**, *47*, 877. f) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res.* **2014**, *47*, 902. g) Shi, M. *Acc. Chem. Res.* **2014**, *47*, 913. h) Fensterbank, L.; Malacria, M. *Acc. Chem. Res.* **2014**, *47*, 953. i) Brooner, R. E. M.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 11714. j) *Modern Gold Catalyzed Synthesis***;** Hashmi, A. S. K.; Toste, F. D., Eds.; Wiley-VCH: Weinheim, 2012. k) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657. l) Rudolph, M.; Hashmi, A. S. K. *Chem. Commun.* **2011**, *47*, 6536. m) Alcaide, B.; Almendros, P.; Alonso, J. M. *Org. Biomol. Chem.* **2011**, *9*, 4405. n) Bandini, M. *Chem. Soc. Rev.* **2011**, *40*, 1358. o) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. p) Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 5232.

17 Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem. Int. Ed*. **2006**, *45*, 5991.

18 Jiang, X.; Ma, X.; Zheng, Z.; Ma, S. *Chem. Eur. J*. **2008**, *14*, 8572.

ricos en electrones.[19] Curiosamente, esta hidroarilación se ha utilizado en la síntesis de productos naturales incluso antes de que el método se estudiara ampliamente. Así, Nelson y col.[20] utilizaron un catalizador catiónico de oro para activar el aleno de partida y hacerlo susceptible de sufrir el ataque nucleófilo del anillo de pirrol, dando como resultado una tetrahidroindolizina, precursora del alcaloide (–)-Rhazinilam, con elevado rendimiento y una excelente transferencia de quiralidad (Esquema II.4). Parece razonable suponer que la doble coordinación del catalizador de oro al doble enlace alénico y al grupo carbonilo es la clave de la alta diastereoselectividad, ya que los catalizadores de paladio y plata o bien no conducen a la ciclación deseada o la dan con bajas diastereoselectividades.



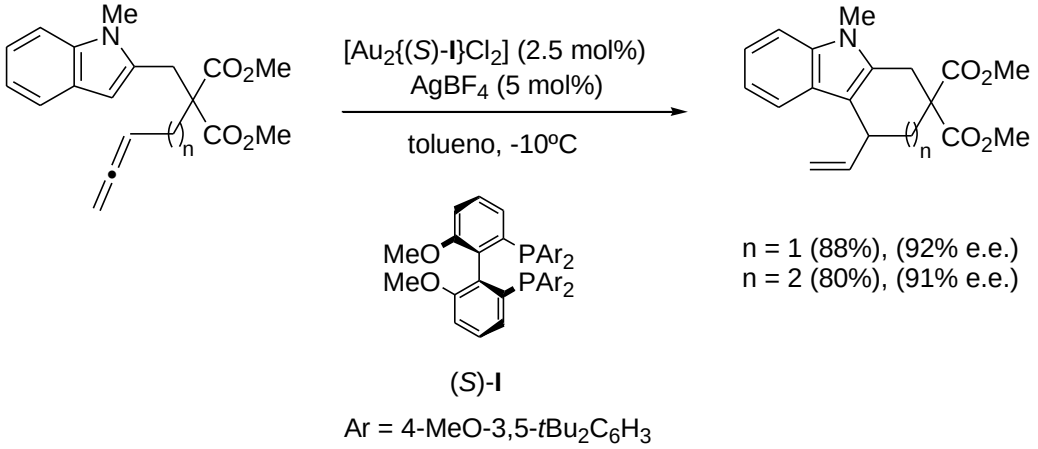
Esquema II.4

Widenhoefer fue el primero en describir la síntesis de tetrahidrocarbazoles y derivados por reacción de hidroarilación intramolecular utilizando alenil indoles como precursores. Partiendo de alenos aquirales, obtienen productos de hidroarilación tricíclicos con buenos rendimientos y altos excesos enantioméricos, utilizando para ello el precatalizador quiral $[Au_2\{(S)\text{-}\mathbf{I}\}Cl_2]$ y tetrafluoroborato de

19 a) Alcaide, B.; Almendros, P.; Alonso, J. M.; Quirós, M. T.; Gadziński, P. *Adv. Synth. Catal.* **2011**, *353*, 1871. b) Kong, W.; Fu, C.; Ma, S. *Chem. Eur. J.* **2011**, *17*, 13134. c) Shapiro, N. D.; Rauniyar, V.; Hamilton, G. L.; Wu, J.; Toste, F. D. *Nature* **2011**, *470*, 245.

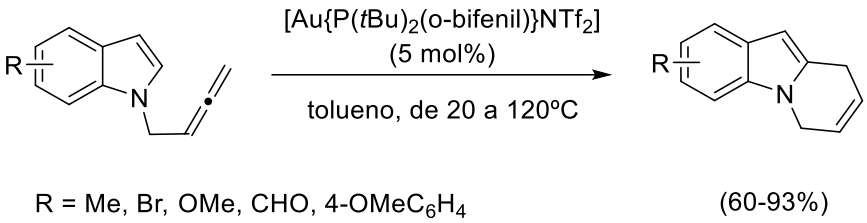
20 Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc*. **2006**, *128*, 10352.

plata (Esquema II.5).[21] Este método permite la formación de carbociclos de seis y siete eslabones.



Esquema II.5

El grupo de Barluenga fue el primero en utilizar *N*-alenil-indoles como materiales de partida para dar lugar a pirido[1,2-*a*]-1*H*-indoles, por reacción de hidroarilación 6-*endo* catalizada por oro (Esquema II.6).[22] La reacción exhibió una alta tolerancia a diferentes grupos funcionales en todas las posiciones del indol, excepto en C2, donde fue necesaria la presencia de un átomo de hidrógeno.



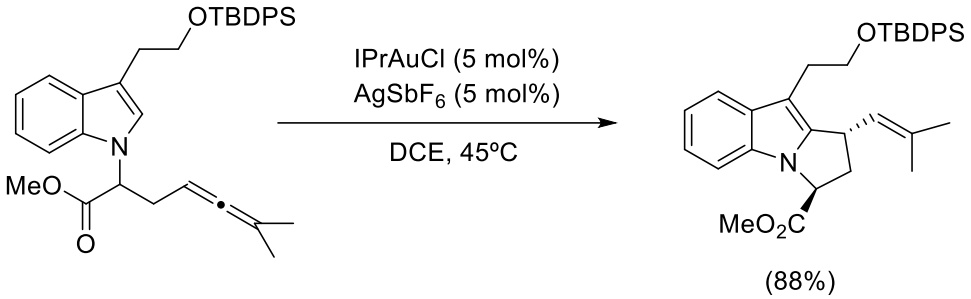
Esquema II.6

Por su parte, Toste y col. describieron la formación de carbociclos de cinco eslabones obteniendo pirrolidinas fusionadas a partir de alenil-indoles, utilizando el carbeno *N*-heterocíclico IPrAuSbF$_6$ como precatalizador. La reacción de

21 a) Liu, C.; Widenhoefer, R. A. *Org. Lett*. **2007**, *9*, 1935. b) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, H.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066.

22 Barluenga, J.; Piedrafita, M.; Ballesteros, A.; Suárez-Sobrino, A. L.; González, J. M. *Chem. Eur. J.* **2010**, *16*, 11827

hidroarilación exhibió una excelente estereoselectividad, obteniéndose los productos como únicos diasteréomeros con buenos rendimientos (Esquema II.7).[23]



Esquema II.7

Nuestro grupo de investigación describió la utilización de catalizadores de Au(I) para la preparación de carbazoles a partir de alenil-indoles tanto NH como N-protegidos.[24] La reacción resultó ser efectiva en ambos casos, observándose exclusivamente la formación de los productos de *C*-ciclación frente a los de *N*- u *O*-ciclación (Esquema II.8).

Esquema II.8

Recientemente, utilizando esta misma metodología Ma y col. describieron la síntesis de diversos alcaloides naturales que presentan el núcleo de carbazol en su estructura (Esquema II.9).[25] Esta nueva ruta de síntesis presenta grandes ventajas como la asequibilidad de los materiales de partida, una gran economía atómica y una alta selectividad.

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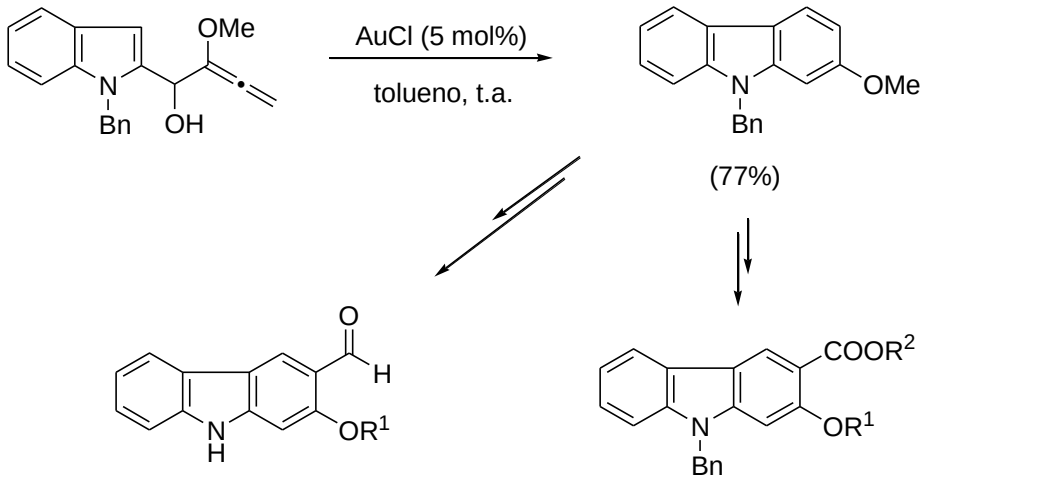
23 Zeldin, R. M.; Toste, F. D. *Chem. Sci.* **2011**, *2*, 1706.

24 a) Véase referencia 19a. Para la carbociclación de 2-alenilindoles véase: b) Alcaide, B.; Almendros, P.; Alonso, J. M.; Fernández, I. *J. Org. Chem*. **2013**, *78*, 6688.

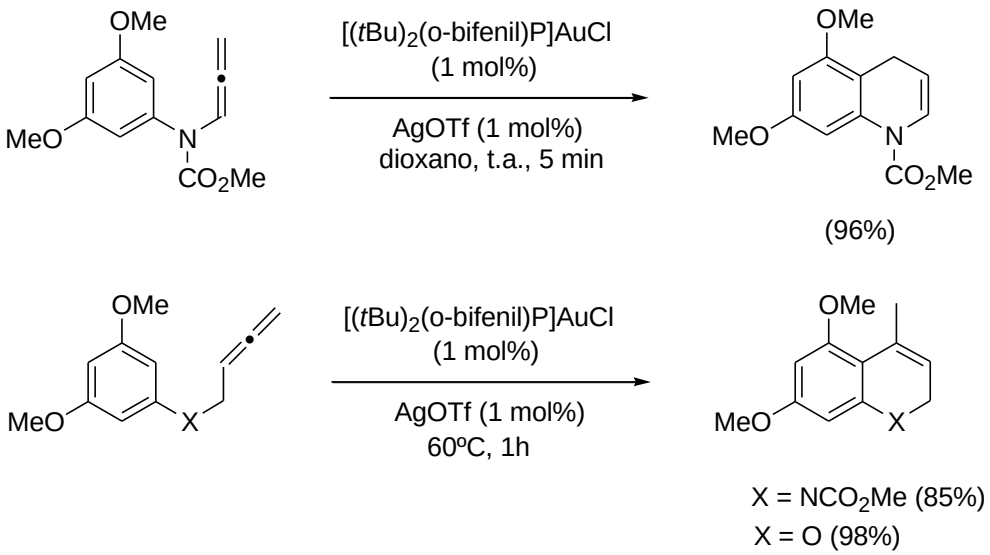
25 a) Qiu, Y.; Ma, D.; Fu, C.; Ma, S. *Org. Biomol. Chem.* **2013**, *11*, 1666. b) Kong, W.; Fu, C.; Ma, S. *Chem. Eur. J.*, **2011**, *17*, 13134.



Esquema II.9

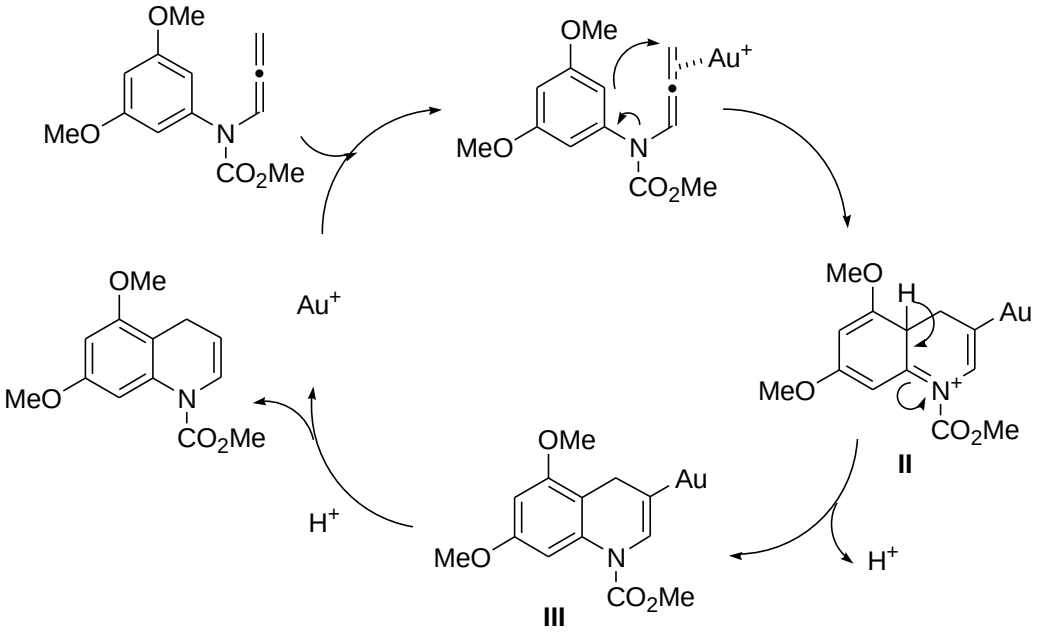
Como se ha comentado anteriormente, los anillos aromáticos ricos en electrones también se pueden utilizar como nucleófilos en las reacciones de hidroarilación de alenos catalizadas por oro. Así, Fuiji, Ohno y col. desarrollaron una ruta eficiente para la formación de dihidroquinolina y derivados de cromeno a partir de aril-alenamidas y aril-éteres alénicos respectivamente, empleando un catalizador catiónico de oro (Esquema II.10).[26] Dependiendo de la estructura del sustrato, el ataque nucleófilo se puede producir tanto en el carbono alénico terminal como en el central. De esta forma, a partir de la alenamida que se muestra en el Esquema II.10 se obtuvo una dihidroquinolina con un 96% de rendimiento, por ciclación 6-*endo*, mientras que los sustratos con un átomo de carbono más entre el aleno y el anillo aromático reaccionaron a través de una ciclación 6-*exo* para dar lugar a los correspondientes heterociclos bicíclicos con buenos rendimientos.

26 Watanabe, T.; Oishi, S.; Fujii, N.; Ohno,H. *Org. Lett*. **2007**, *9*, 4821.



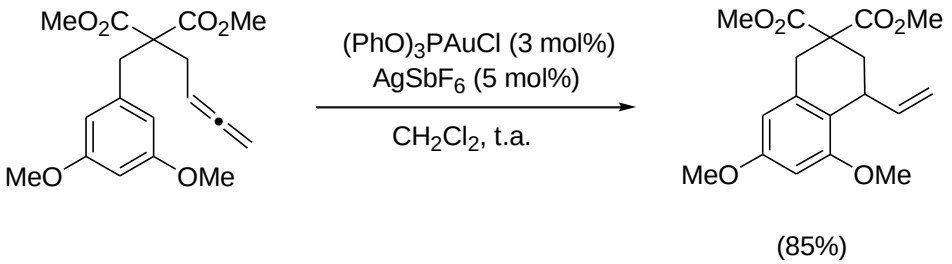
Esquema II.10

El mecanismo propuesto por estos autores consistiría en la activación del aleno mediante la coordinación de la especia catiónica de oro seguido de una sustitución electrófila en el anillo aromático, para dar lugar al complejo catiónico vinil-oro **II**, el cual conduce al intermedio neutro **III** mediante la pérdida de un protón. Finalmente la ruptura del enlace carbono-oro daría lugar a las correspondientes dihidroquinolinas con regeneración de la especie catalíticamente activa (Esquema II.11).



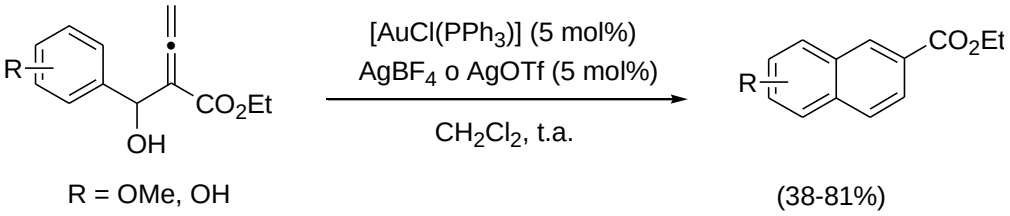
Esquema II.11

De forma análoga, Gagné y col. describieron una ciclación 6-*exo* catalizada por una mezcla de cloruro de trifenilfosfito de oro(I) y hexafluoroantimoniato de plata a partir de aril-alenos, que condujo a tetralinas con altos rendimientos (Esquema II.12).[27]



Esquema II.12

Lee y col. fueron los primeros en describir la preparación de naftalenos diferentemente sustituidos a través de una reacción de carbociclación intramolecular utilizando aril-alenos. Así, la ciclación 6-*endo* de α-hidroxialquil ésteres alénicos condujo a los correspondientes derivados de naftaleno, utilizando una sal de oro como catalizador (Esquema II.13).[28] Una reactividad similar fue descrita por Ma y col. en la síntesis de naftalenos polisustituidos a partir de 1-arilalca-2,3-dienilacetatos utilizando el mismo sistema catalítico y 1,4-dioxano como disolvente.[29]



R = OMe, OH

(38-81%)

Esquema II.13

Recientemente el grupo de Ma desarrolló un método eficaz para la síntesis de 1,4-dihidroarenos con un centro quiral en su estructura, a través de una

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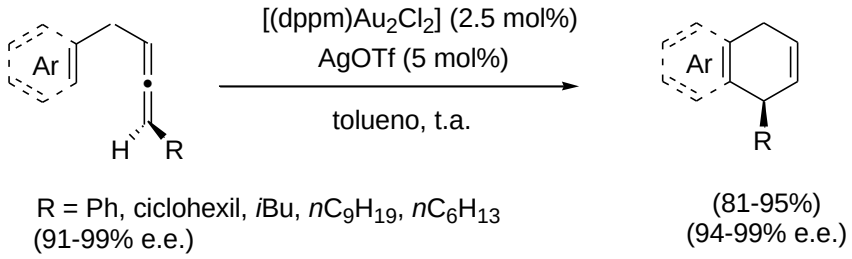
27 a) Weber, D.; Tarselli, M. A.; Gagné, M. R. *Angew. Chem*. **2009**, *121*, 5843; *Angew. Chem., Int. Ed*. **2009**, *48*, 5733. b) Weber, D.; Gagné, M. R. *Org. Lett*. **2009**, *11*, 4962. c) Tarselli, M. A.; Gagné, M. R. *J. Org. Chem*. **2008**, *73*, 2439

28 Park, C.; Lee, P. H. *Org. Lett.* **2008**, *10*, 3359.

29 Kong, W.; Fu, C.; Ma, S. *Eur. J. Org. Chem.* **2010**, 6545.

hidroarilación asimétrica 6-*endo* de aril-alenos enantiopuros, utilizando para ello una especie bimetálica de oro y triflato de plata (Esquema II.14).[30]



R = Ph, ciclohexil, *i*Bu, *n*C_9H_{19}, *n*C_6H_{13}
(91-99% e.e.)

(81-95%)
(94-99% e.e.)

Esquema II.14

b) Reacciones de carbociclación catalizadas por paladio

Los catalizadores de paladio han contribuido enormemente al desarrollo de la química de alenos,[31] desde su primera aplicación sintética en la década de los 80.[32] En muchas de estas reacciones, un complejo de aril-, alil- o vinil-Pd(II), generado in situ, a partir de una especie de Pd(0) y un haluro de arilo, alilo o vinilo, respectivamente, puede actuar como fuerza motriz para inducir ciclaciones de alenos que contienen un carbono nucleófilo.[33]

La primera reacción de carbopaladación de alenos con una cadena carbonada nucleófila en su estructura fue descrita en 1985, dando lugar a la formación de ciclopropil y cicopentenil derivados a partir de β-alenilmalonatos. La regioselectividad de la reacción viene determinada por el tamaño del haluro de arilo o vinilo utilizado en cada caso (Esquema II.15).[34]

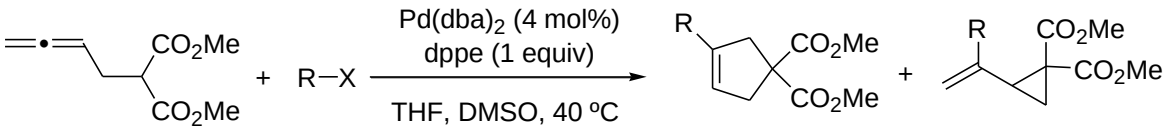
30 Qiu, Y.; Zhou, J.; Li, J.; Fu, C.; Guo, Y.; Wang, H.; Ma, S. *Chem. Eur. J*. **2015**, *21*, 15939.

31 a) Véanse referencias 14b, 14p, 14s y 15b. b) Aubert, C.; Fensterback, L.; Garcia, P.; Malacria,M.; Simonneau, A. *Chem. Rev*. **2011**, *111*, 1954. c) Alcaide, B.; Almendros, P.; Martínez del Campo, T. *Chem. Eur. J.* **2010**, *16*, 5836. d) Pinho e Melo, T. M. V. D. *Curr. Org. Chem*. **2009**, *13*, 1406. e) Jeganmohan, M.; Cheng, C.–H. *Chem. Commun*. **2008**, 3101.

32 a) Shimizu, I.;Tsuji, J. *Chem. Lett*. **1984**, 233. b) Hegedus, L. S.; Kambe, N.; Tamura, R.; Woodgate, P. D. *Organometallics* **1983**, *2*, 1658.

33 Davies, I. W.; Scopes, D. I. C.; Gallagher, T. *Synlett*. **1996**, *85*.

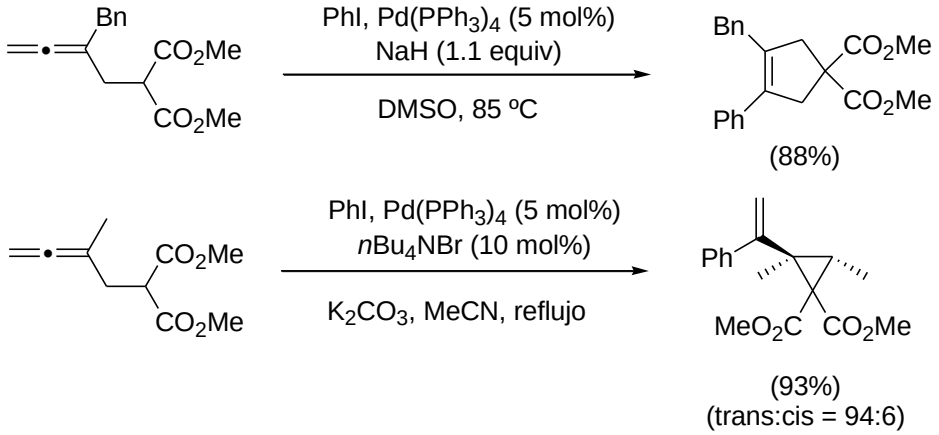
34 a) Ahmar, M.; Cazes, B.; Goré, J. *Tetrahedron* **1987**,*43*, 3453. b) Ahmar, M.; Cazes, B.; Goré, J. *Tetrahedron Lett.* **1985**, *26*, 3795.



RX = Iodobenceno	(65%)	100	:	0
RX = 1-Bromoeteno	(80%)	0	:	100
RX = 1-Bromociclohexeno	(50%)	96	:	4

Esquema II.15

Los grupos de Ma y Oh continuaron con el estudio de estas transformaciones, consiguiendo de forma exclusiva la obtención de ciclopentenos, en presencia de hidruro de sodio y $Pd(PPh)_3$. Hay que destacar que los ciclopropanos se obtuvieron de forma regio- y estereoselectiva simplemente modificando las condiciones de reacción y los sustituyentes de la posición interna de los alenos de partida (Esquema II.16).[35]



Esquema II.16

Trost y col. fueron los primeros en describir la síntesis de ciclos de más de cinco eslabones a través de una reacción de carbociclación de alenos catalizada por paladio. El ataque nucleófilo al carbono central alénico condujo a los correspondientes anillos de seis eslabones como únicos regioisómeros con buenos rendimientos (Esquema II.17).[36]

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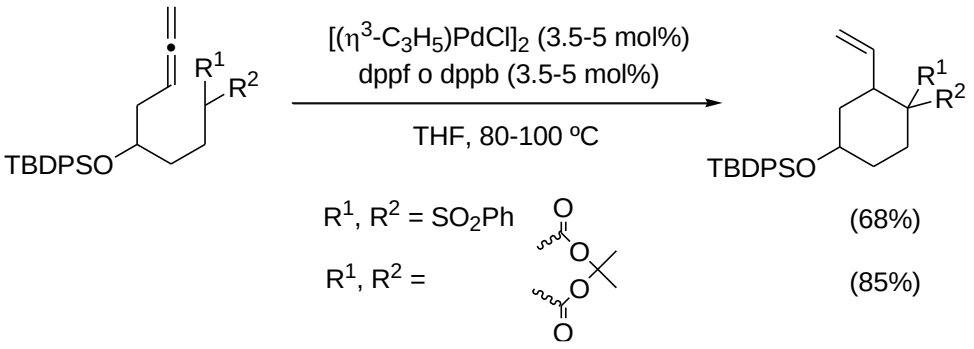
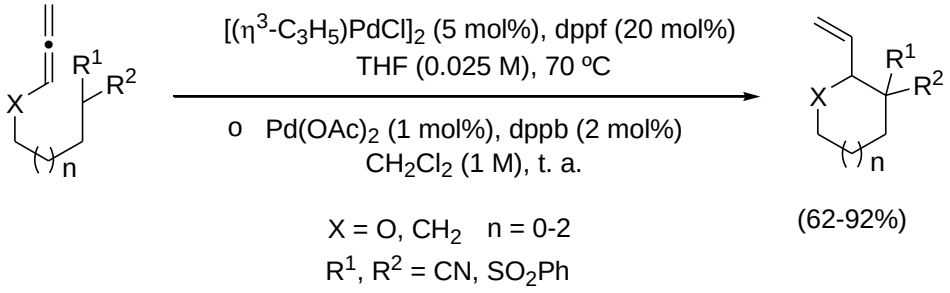
[35] a) Shu, W.; Jia, G.; Ma, S. *Org. Lett.* **2009**, *11*, 117. b) Ma, S.; Jiao, N.; Yang, Q. ; Zheng, Z. *J. Org. Chem.* **2004**, *69*, 6463. c) Ma, S.; Jiao, N.; Zhao,S.; Hou, H. *J. Org. Chem.* **2002**, *67*, 2837. d) Oh, C. H.; Rhim, C. Y.; Song, C. H.; Ryu, J. H. *Chem. Lett.* **2002**, *31*, 1140. e) Ma, S.; Zhao, S. *Org. Lett.* **2000**, *2*, 2495.

[36] Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156.



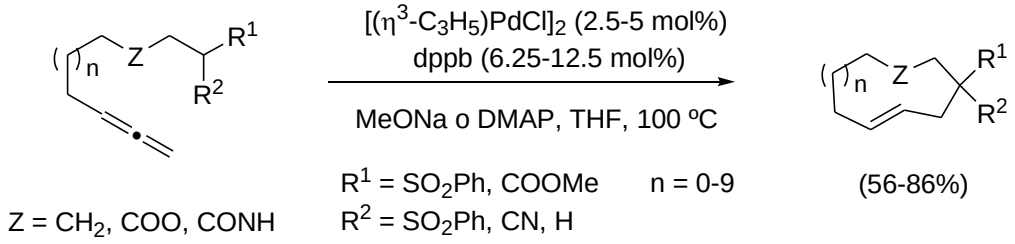
Esquema II.17

De forma análoga, el grupo de Yamamoto desarrolló un método de obtención de ciclos de cinco a siete eslabones con buenos rendimientos, utilizando como materiales de partida alenos que presentaban un centro nucleófilo en su estructura separado por un fragmento de 3 a 5 carbonos del resto alénico (Esquema II.18).[37]



Esquema II.18

Esta metodología fue utilizada por Trost y col. en la síntesis de carbociclos, lactamas y lactonas, de 9 a 17 eslabones, ampliando la cadena carbonada presente entre el nuleófilo y el aleno (Esquema II.19).[38]

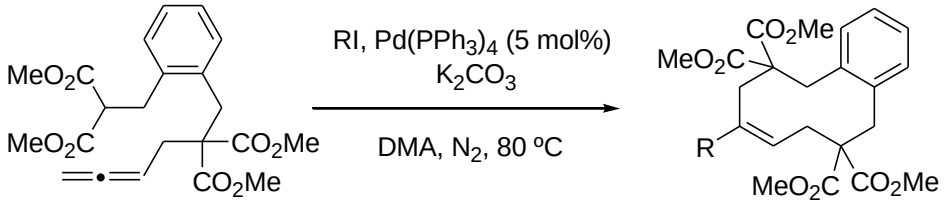


Esquema II.19

37 a) Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 1747. b) Meguro, M.; Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 7453.

38 Trost, B. M.; Michellys, P.–Y.; Gerusz, V. J. *Angew. Chem. Int. Ed.* **1997**, *36*, 1750

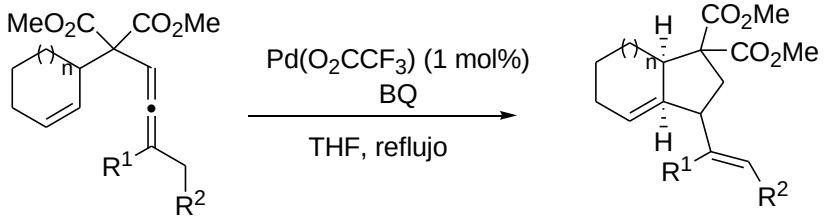
Ma y col. por su parte, desarrollaron un método para la preparación regio- y estereoselectiva de carbociclos de más de nueve eslabones fusionados a un anillo de benceno por reacción de carbopaladación con diferentes yoduros de arilo y alquenilo (Esquema II.20).[39]



R = Ph, 4-YC_6H_4 (Y = Me, OMe, Ac, Cl), 4-piridilo, (*E*)-estirilo, (*E*)-1-hexenilo (60-91%)

Esquema II.20

El grupo de Bäckvall fue el primero en introducir la utilización de condiciones oxidantes en este tipo de reacciones, describiendo la ciclación de 1,3-dienil- y alquenil-alenos sustituidos para dar lugar a [4.3.0]- y [5.3.0]-biciclos (Esquema II.21).[40] La reacción transcurre con una alta estereoselectividad, y puede llevarse a cabo reemplazando la benzoquinona por atmósfera de oxígeno.



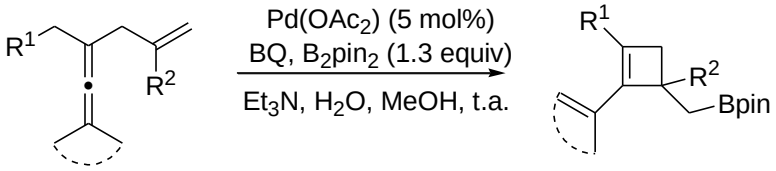
R^1 = Me, R^2 = H
R^1, R^2 = $(CH_2)_4$ n = 1-3 (73-94%)

Esquema II.21

39 Jiang, X.; Yang, Q.; Yu, Y.; Fu, C.; Ma, S. *Chem. Eur. J*. **2009**, *15*, 7283.

40 a) Bartholomeyzik, T.; Mazuela, J.; Pendrill, R.; Deng, Y.; Bäckvall, J.–E *Angew. Chem. Int. Ed.* **2014**, *53*, 8696. b) Deng, Y.; Bartholomeyzik, T.; Bäckvall, J.–E. *Angew. Chem. Int. Ed.* **2013**, *52*, 6283. c) Deng, Y.; Bartholomeyzik, T.; Persson, A. K. A.; Sun, J.; Bäckvall, J.–E. *Angew. Chem. Int. Ed.* **2012**, *51*, 2703. d) Persson, A. K. A.; Jiang, T.; Johnson, M. T.; Bäckvall, J.–E. *Angew. Chem. Int. Ed.* **2011**, *5*0, 6155. e) Franzén, J.; Bäckvall, J.–E. *J. Am. Chem. Soc.* **2003**, *125*, 6056. f) Löfstedt, J.; Franzén, J.; Bäckvall, J.–E. *J. Org. Chem.* **2001**, *66*, 8015. Para la versión enantioselectiva de la reacción véase: g) Jiang, T.; Bartholomeyzik, T.; Mazuela, J.; Willersinn, J.; Bäckvall, J.–E. *Angew. Chem. Int. Ed.* **2015**, *54*, 6024.

Recientemente, el mismo grupo de investigación ha desarrollado un método selectivo de síntesis de ciclobutenos por reacción de carbociclación oxidante seguida de borilación de enalenos catalizada por paladio (Esquema II.22).[41] La reacción exhibió buenos rendimientos y una gran tolerancia a grupos funcionales.

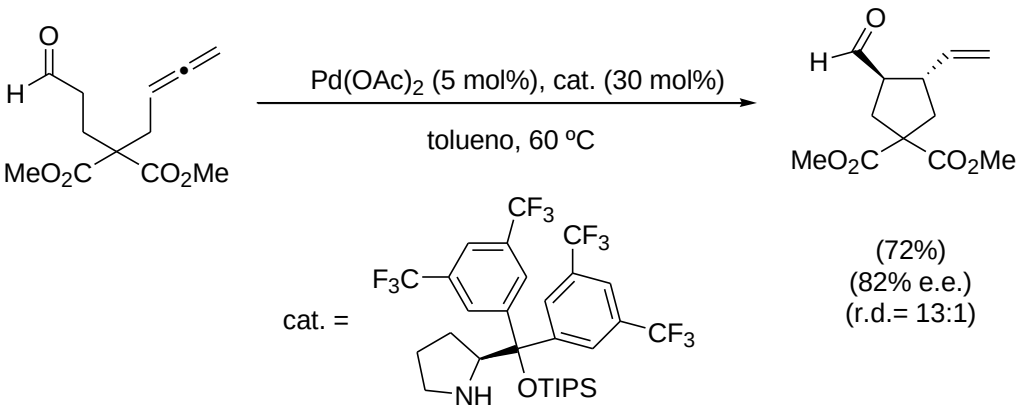


R^1 = CO_2Et, Ph, C_3H_7, CH_2OTs, CH_2OBn, CH_2OH, ciclohexilo, NFtalimida (40-84%)

R^2 = H, Me

Esquema II.22

Por su parte, Dixon y col. llevaron a cabo una carbociclación diastereo- y enantioselectiva de alenales y alenonas obteniendo ciclopentanos diferentemente sustituidos por combinación de catálisis metálica y organocatálisis (Esquema II.23).[42]



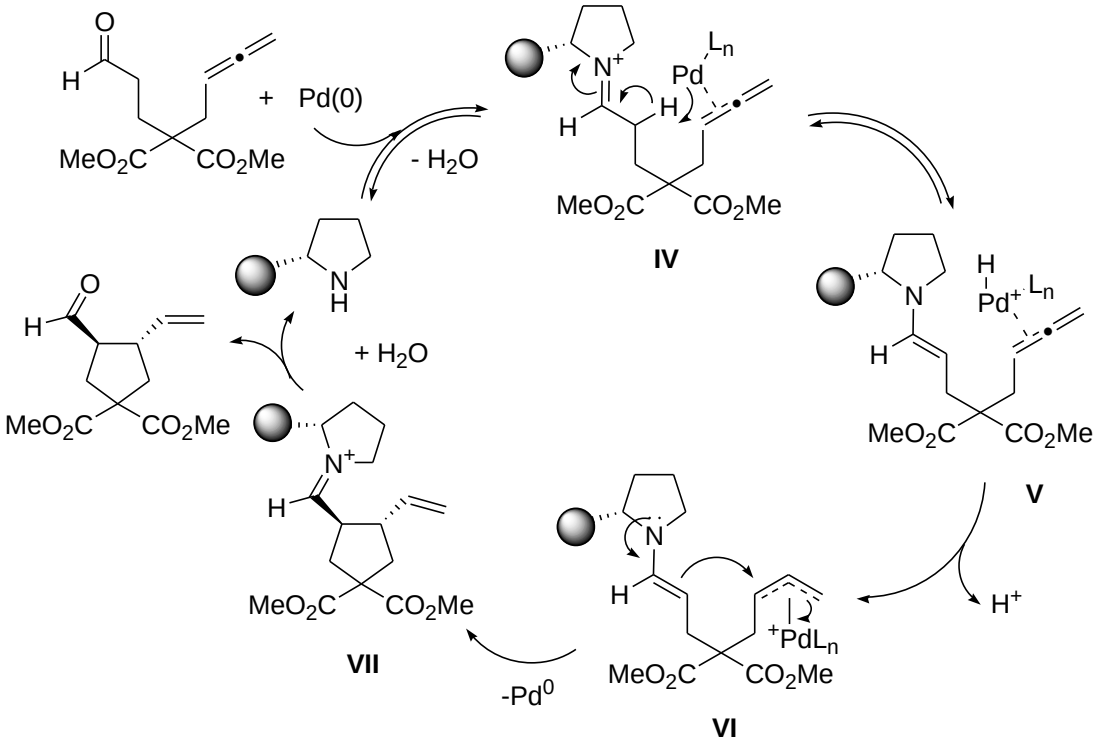
(72%)
(82% e.e.)
(r.d.= 13:1)

Esquema II.23

El mecanismo propuesto para esta nueva reacción de carbociclación implicaría en primer lugar una condensación rápida y reversible entre el organocatalizador y el aleno de partida junto con la complejación del Pd(0) para dar

[41] Qiu, Y.; Yang, B.; Zhu, C.; Bäckvall, J.–E. *Angew. Chem. Int. Ed.* **2016**, *55*, 6520.
[42] Li, M.; Datta, S.; Barber, D. M.; Dixon, D. J. *Org. Lett*. **2012**, *14*, 6350.

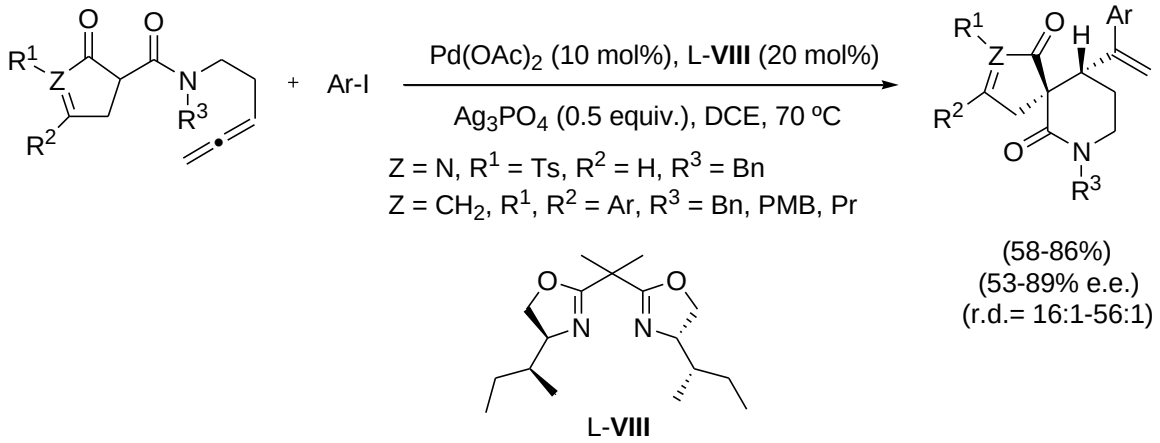
lugar al intermedio catiónico imínico **IV**. A continuación la especie de Pd(0) es la encargada de abstraer el hidrógeno de la posición α del catión iminio lo que conduce a la formación de la imina **V**, que presenta un complejo hidropaladio(II)-aleno en su estructura. La subsiguiente hidropaladación del sustituyente alénico generaría el complejo π-alil **VI**, el cual sufre el ataque nucleófilo intramolecular de la enamina para formar el ion imínico **VII**. La hidrólisis final daría lugar a los correspondientes ciclopentanos con regeneración tanto del organocatalizador como el catalizador metálico (Esquema II.24).



Esquema II.24

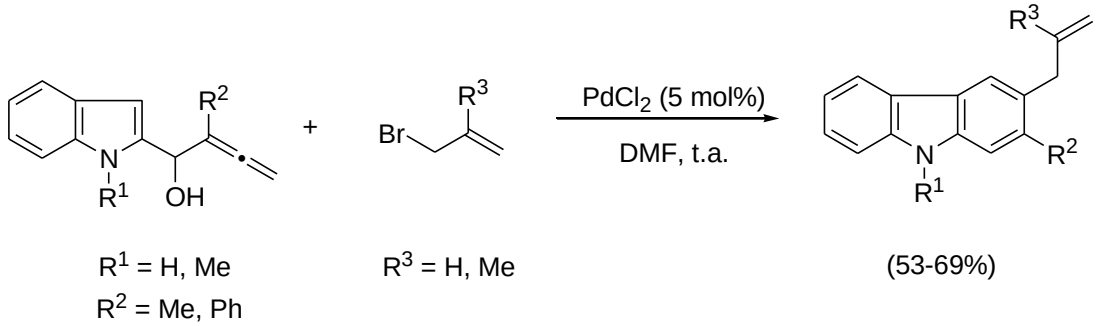
El mismo grupo logró la síntesis enantioselectiva de espirolactamas sustituidas por reacción de carbociclación en cascada utilizando fosfato de plata, $Pd(OAc)_2$ y ligandos quirales de bisoxazolina. La reacción exhibió buenos rendimientos y una alta enantio- y diastereoselectividad (Esquema II.25).[43]

[43] Li, M; Hawkins, A.; Barber, D. M.; Bultnick, P.; Herrebout, W.; Dixon, D. J. *Chem. Commun.* **2013**, *49*, 5265.



Esquema II.25

Nuestro grupo de investigación por su parte fue el primero en utilizar paladio como catalizador en reacciones de carbociclación de alenil-indoles. Así, se describió una metodología de preparación de 3-alil-carbazoles a través de una secuencia de carbociclación-acoplamiento catalizada por $PdCl_2$, utilizando como materiales de partida alenil-indoles y haluros orgánicos insaturados diferentemente sustituidos (Esquema II.26).[44]

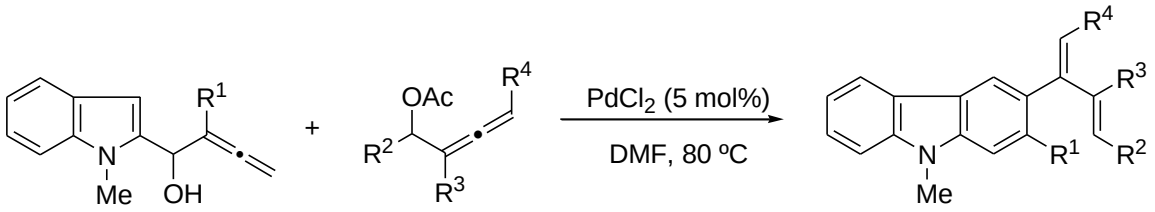


Esquema II.26

De forma análoga, se desarrolló un proceso tándem de carbociclación-acoplamiento cruzado de dos α-alenoles diferentes que permite obtener carbazoles altamente funcionalizados con buenos rendimientos (Esquema II.27).[45] En ambos casos, la reacción dominó de ciclación-acoplamiento fue totalmente regioselectiva, no observándose productos de *O*-ciclación.

[44] Véase referencia 19a.

[45] Alcaide, B.; Almendros, P.; Alonso, J. M.; Fernández, I. *Chem. Commun.* **2012**, *48*, 6604.



R^1 = Me, H R^2 = H, Ph, 4-$OMeC_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4 (40-71%)

R^3 = H, Me R^4= H, Ph, *n*Pr, *t*Bu

Esquema II.27

II.1.2. Reacciones de transposición tipo Meyer-Schuster en alenos

La utilización de cetonas α,β-insaturadas como materiales de partida para la síntesis de una gran variedad de compuestos, así como su presencia en muchos productos naturales con actividad biológica, justifica el interés por desarrollar nuevos métodos para la síntesis de estos compuestos.[46]

Una metodología alternativa a los métodos clásicos de preparación de cetonas α,β-insaturadas, como puede ser la condensación aldólica, es la reacción de transposición de Meyer-Schuster, donde un alcohol propargílico sufre un desplazamiento 1,3 del grupo hidroxilo seguido de tautomerización.[47]

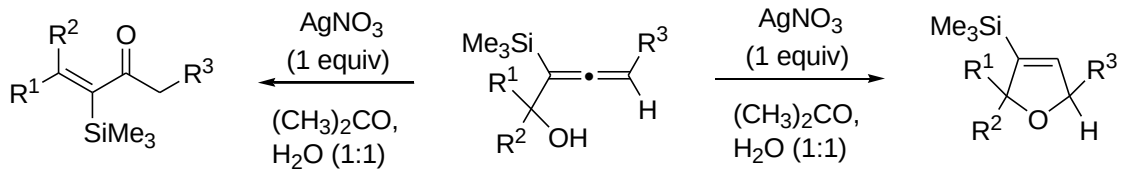
En este contexto, la transposición de alcoholes alénicos podría representar una nueva ruta efectiva de síntesis de cetonas α,β-insaturadas, pudiéndose obtener ahora enonas conjugadas sustituidas en la posición interna. Sin embargo, en la literatura únicamente existen algunos ejemplos aislados de la citada transformación, los cuales se expondrán a continuación.

Wang y col. fueron los primeros en aislar cetonas α,β-insaturadas, con bajos rendimientos, a partir de α-alenoles, en su estudio de oxiciclación de

46 a) Sahu, N. K.; Balbhadra, S. S.; Choudhary, J.; Kohli, D. V. *Curr. Med. Chem.* **2012**, *19*, 209. b) Glorius, E. F. *Science of Synthesis, Vol. 25;* Brückner R., Ed.; Georg Thieme: Stuttgart, 2007, 733. c) Escher, I.; Glorius, E. F. *Science of Synthesis, Vol. 25;* Brückner R.; Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 2006, 733. d) Foster, C. E.; Mackie, P. R.; *Comprehensive Organic Functional Group Transformations II*, Vol. 3; Katritzky, A. R.; Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005, 215. e) Takeda, T.; *Modern Carbonyl Olefination*; Wiley-VCH: Weinheim, 2004. f) Rowe, D. J. *Perfum. Flavor* **2000**, *25*, 1. g) Otera, J. *Modern Carbonyl Chemistry*; Wiley-VCH: Weinheim, 2000.

47 a) Bauer, E. B. *Synthesis* **2012**, *44*, 1131. b) Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, *7,* 4149.

trimetilsililalenoles catalizada por plata (Esquema II.28).[48] Los autores propusieron la formación de un carbocatión terciario, estabilizado por hiperconjugación gracias al grupo TMS, seguida del ataque de una molécula de agua al carbono central alénico para explicar la formación de las enonas conjugadas. Se observó que el rendimiento de estos compuestos aumentó al disminuir el impedimento estérico del material de partida.



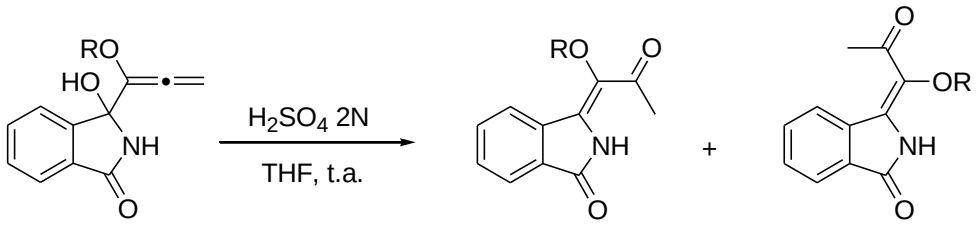
R^1 = Me, $-(CH_2)_5-$ | R^1 = H, $-(CH_2)_5-$

R^2 = Me, $-(CH_2)_5-$ | R^2 = Me, Ph, *i*Pr, *n*Pent, $-(CH_2)_5-$

R^3 = H, *n*Pr | R^3 = *n*Pr

Esquema II.28

En la literatura no aparece ningún ejemplo adicional de esta transformación hasta el año 2006, cuando el grupo de Reissig obtuvo casualmente cetonas α,β-insaturadas por tratamiento de alenil-indoles con ácido sulfúrico (Esquema II.29).[49] La proporción *Z*/*E* de la alquenona depende del sustituyente alcoxilo del material de partida.

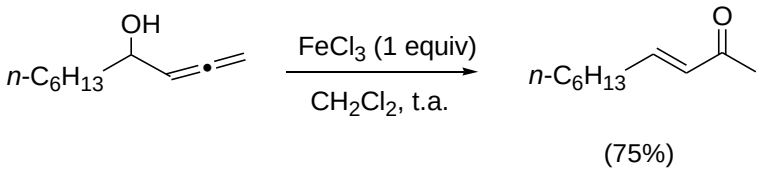


Esquema II.29

En el mismo año, el grupo de Padrón y Martín desarrollando un acoplamiento entre alcoholes homopropargílicos y aldehídos catalizado por $FeCl_3$,

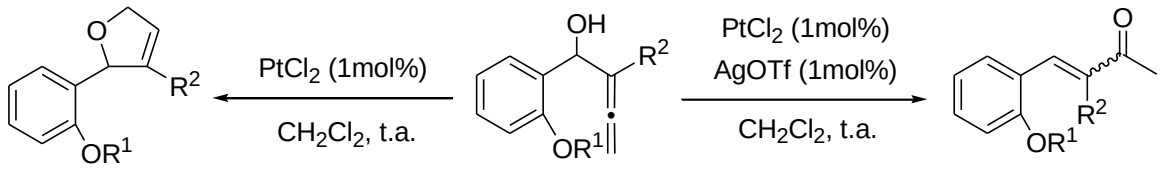
[48] Nikam, S. S.; Chu, K. H.; Wang, K. K. *J. Org. Chem*. **1986**, *51*, 745.
[49] Kaden, S.; Reissig, H.–U.; Brüdgam, I.; Hartl, H. *Synthesis* **2006**, 1351.

describieron la síntesis de un ejemplo de cetona α,β-insaturada, la dec-3-en-2-ona, a partir del α-hidroxialeno correspondiente (Esquema II.30).[50]



Esquema II.30

Recientemente, nuestro grupo de investigación describió una nueva metodología para la síntesis de cetonas α,β-insaturadas partiendo de α-alenoles derivados del salicilaldehído y empleando un sistema catalítico bimetálico de Pt(II)-Ag(I) (Esquema II.31).[51] La obtención divergente de furanos y enonas puso de manifiesto el importante papel de la sal de plata en la activación del precatalizador de platino.



(47-64%)

R^1 = Me, alilo, metilalilo, 2-propinilo, 2-butinilo
R^2 = Me, Ph, 4-$MeOC_6H_4$

(19-84%)

Esquema II.31

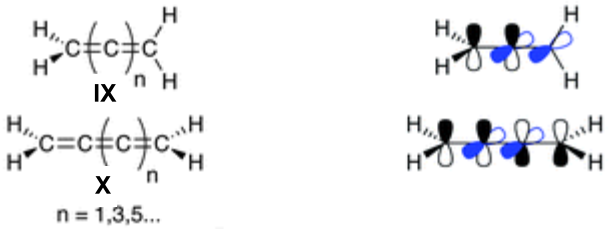
II.2. Síntesis y reactividad de [3]-cumulenoles

Las moléculas que presentan dobles enlaces consecutivos en su estructura han dado lugar a un gran número de investigaciones desde que tuvo lugar la síntesis del primer aleno hace ya más de un siglo.[52] En este tiempo la química de alenos ha experimentado un gran desarrollo, como ha quedado patente en la revisión bibliográfica anterior, mientras que sus homólogos superiores, los

50 Miranda, P. O.; Ramírez, P. A.; Padrón, J. I.; Martín, V. S. *Tetrahedron Lett*. **2006**, *47*, 283.
51 Alcaide, B.; Almendros, P.; Fernández, I.; Martínez del Campo, T.; Naranjo, T. *Adv. Synth. Catal.* **2013**, *355*, 2681.
52 Véase referencia 11.

cumulenos, han dado lugar a un número significativamente menor de ejemplos.[53] La falta de estudios sobre estos compuestos se debe probablemente a la dificultad en la preparación de los materiales de partida y a la posibilidad de obtener un gran número de isómeros diferentes del aducto deseado.

El término "cumuleno" se refiere a los hidrocarburos, y sus derivados formados por sustitución, que presentan dos o más dobles enlaces C–C consecutivos en su estructura, sin diferenciar los compuestos que presentan un número impar de carbonos en el sistema conjugado, tipo **IX** o tipo alenos, de los que presentan un número par, tipo **X** (Esquema II.32). Su principal diferencia radica en la quiralidad, ya que mientras los cumulenos con número par de carbonos son planos y no pueden llegar a presentar quiralidad axial, los que cuentan con un número impar (tipo alenos), sí pueden ser quirales.[54]



Esquema II.32

Esta posible quiralidad axial, junto con su interesante reactividad, pudiéndose comportar como nucleófilos, electrófilos y en ocasiones, dienófilos; así como sus importantes propiedades fotofísicas han hecho a estos compuestos muy útiles en síntesis orgánica y química de los materiales.[55]

Entre ellos, los cumulenos de menor tamaño o [3]cumulenos, con tres dobles enlaces consecutivos, han despertado recientemente un gran interés por sus potenciales aplicaciones en el diseño de fármacos antitumorales[56] y sus ya

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53 a) Para revisiones de cumulenos véanse: Januszewski, J. A.; Tykwinski, R. R. *Chem. Soc. Rev.* **2014**, *43*, 3184. b) Leroyer, L.; V. Maraval, V.; Chauvin, R. *Chem. Rev*. **2012**, *112*, 1310. c) Ogasawara, M. *Science of Synthesis. Cumulenes and Allenes*, Vol. 44.1; Bellus, D., Ed.; Georg Thieme Verlag, 2008, 9. d) Bruneau, C.; Renaud, J.–L. *Compr. Org. Funct. Group Transform. II*, Vol. 1.20; Katritzky, A.R.; Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005, 1019.

54 Hendon, C. H.; Tiana, D.; Murray, A. T.; Carbery, D. R.; Walsh, A. *Chem. Sci.* **2013**, *4*, 4278.

55 a) Januszewski, J. A.; Wendinger, D.; Methfessel, C. D.; Hampelvand, F.; Tykwinski, R. R. *Angew. Chem. Int. Ed*. **2013**, 1817. b) Kato, S.–I.; Takahashi, N.; Nakamura, Y. *J. Org. Chem.* **2013**, *78*, 7658. c) Li, Y.; Köse, M. E.; Schanze, K. S. *J. Phys. Chem. B* **2013**, *117*, 9025. d) Ohashi, S.; Inagaki, S. *Tetrahedron* **2001**, *57*, 5361.

56 Véase referencia 3.

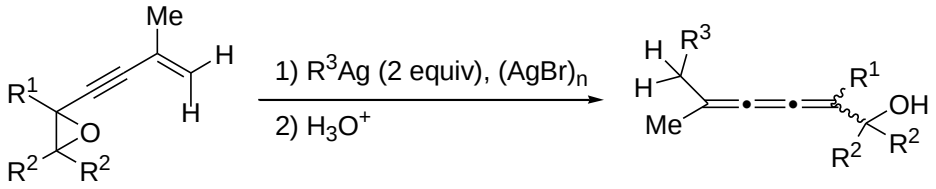
citadas propiedades eléctricas y fotofísicas, que les convierte en excelentes candidatos para el desarrollo de cables moleculares, sistemas ópticos no lineales, ferromagnéticos, polímeros conjugados, etc.[57] Además, representan intermedios muy útiles para la creación de redes de carbonos bidimensionales como los radialenos.[58]

Una vez enmarcado el contexto, a continuación se llevará a cabo un resumen de las síntesis descritas hasta la fecha de [3]cumulenos que presentan un grupo hidroxilo en su estructura, los [3]cumulenoles, y de los escasos ejemplos descritos de su reactividad.

II.2.1. Síntesis de [3]-cumulenoles

Aunque en los últimos años se han descrito un mayor número de métodos de síntesis de cumulenos,[59] existen muy pocos ejemplos en la literatura de metodologías de preparación de [3]-cumulenoles funcionalizados.

Vermeer y col. fueron los primeros en describir la formación de 2,3,4-trien-1-oles, a partir de buteniniloxiranos y organometálicos de plata (Esquema II.33).[60] La reacción, en la que está involucrada una apertura de epóxido, exhibió mejores rendimientos cuando se utilizaban reactivos de plata estéricamente menos impedidos.



R^1 = H, R^2 = Me
R^1 = Me, R^2 = H

R^3 = *n*Bu, *t*Bu, *i*Pr
n = 0-1

(50-90%)

Esquema II.33

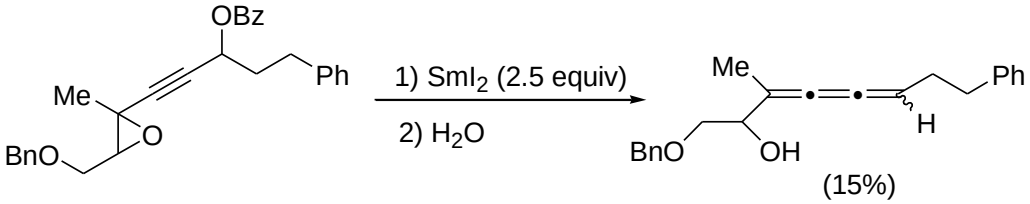
[57] a) Véase referencia 4. b) Kinoshita, I.; Kijima, M.; Shirakawa, H. Macromol. *Rapid Commun*. **2000**, *21*, 1205. c) Kijima, M.; Kinoshita, I.; Shirakawa, H. *Synth. Met.* **1999**, *101*, 145.

[58] a) Diederich, F.; Rubin,Y. *Angew. Chem. Int. Ed.* **1992**, *31*, 1101. b) Iyoda, M.; Tanaka, S.; Otani, H.; Nose, M.; Oda, M. *J. Am. Chem. Soc.* **1988**, *110*, 8494.

[59] a) Véase referencia 53. b) Hopf, H. *Classics in Hydrocarbon Chemistry*; Wiley-VCH: Weinheim, 2000, 171. c) Chow, H.–K.; Cao, X.–P.; Leung, M.–K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 193. d) Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier: New York, 1981. e) Hopf, H. *The Chemistry of Ketenes, Allenes and Relates Compounds Part 2*, Chapter 20; Patai, S., Eds.; John Wiley & Sons: New York, 1980.

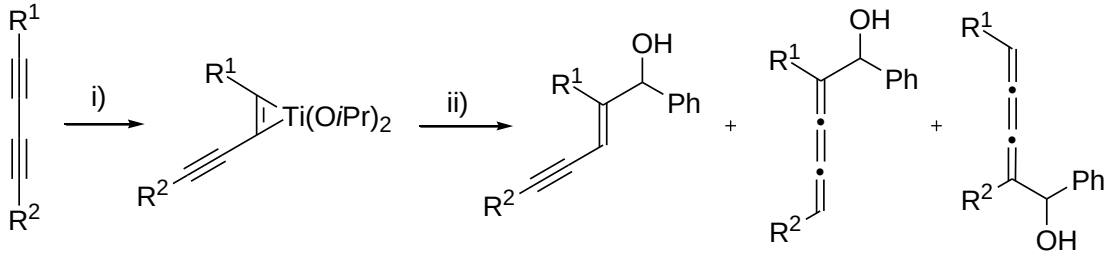
[60] Tigchelaar, M.; Meijer, J.; Kleijn, H.; Bos, H. J. T.; Vermeer, P. *J. Organomet. Chem*. **1981**, *221*, 117.

Utilizando materiales de partida muy similares, Aurrecoechea y col. detectaron mediante ^{1}H-RMN la formación de [3]cumulenoles en su intento de obtener furanos trisustituidos a partir de 4,5-epoxi-2-alquinil-ésteres, en una reacción promovida por SmI_2 (Esquema II.34). [61] Los autores sólamente consiguieron aislar y caracterizar un único derivado de 2,3,4-trien-1-ol.



Esquema II.34

El grupo de Sato por su parte describió la formación de estos compuestos junto a los eninos que se muestran en el Esquema II.35, por reacción de titanación de 1,3-diinos seguida de un ataque nucleófilo del complejo acetileno-titanio al benzaldehído.[62]



$R^1 = CO_2tBu$, $R^2 = C_6H_{13}$ (57%)	55	:	0	:	45
$R^1 = Me_3Si$, $R^2 = Me_3Si$ (79%)	79	:	21	:	0

i) $Ti(OiPr)_4$ (1.25 equiv) / *i*PrMgCl (2.5 equiv) ii) PhCHO

Esquema II.35

Combinando la misma metodología anterior con el uso de ácidos de Lewis, Liu y col. describieron la síntesis estereoselectiva de *cis*-2,3,4-trien-1-oles (Esquema II.36). [63] La reacción exhibió buenos rendimientos con una gran diversidad de aldehídos y cetonas.

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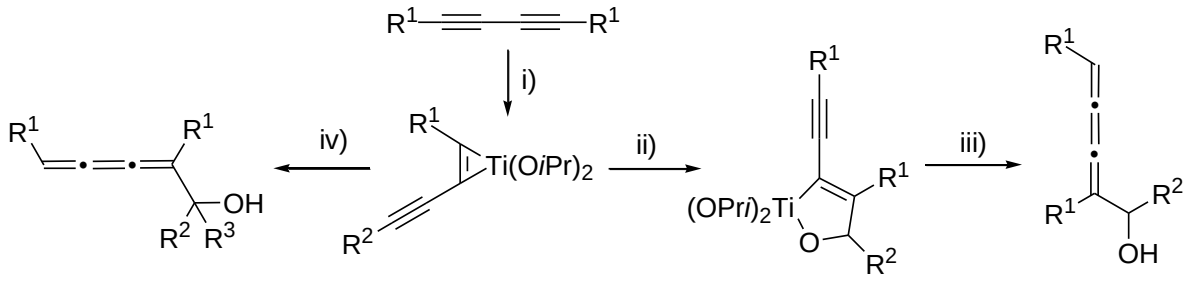
61 a) Aurrecoechea, J. M.; Pérez, E. *Tetrahedron* **2004**, *60*, 4139. b) Aurrecoechea, J. M.; Pérez, E.; Solay, M. *J. Org. Chem.* **2001**, *66*, 564.

62 Delas, C.; Urabe, H.; Sato, F. *Chem. Commun.* **2002**, 272.

63 Chen, J.; Liu, Y. *Organometallics* **2010**, *29*, 505.



(26-77%)

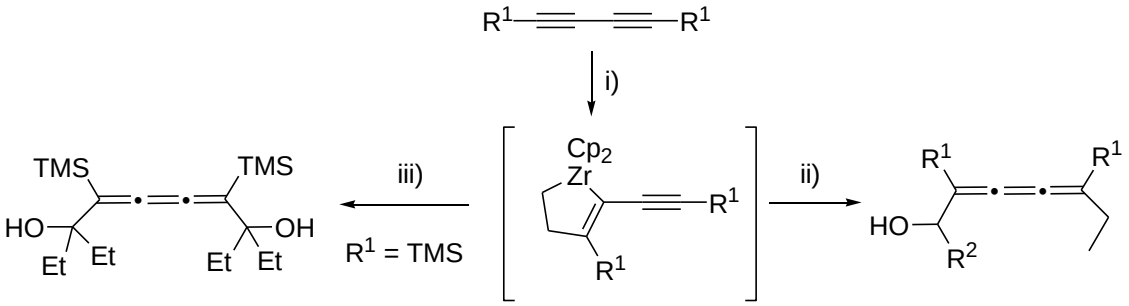
R^1 = TMS, TBS, Ph
R^2 = Ph, *i*Pr,4-YC_6H_4 (Y = Me, OMe, Cl), 2-tiofenilo, ciclohexilo
R^3 = Me, Ph, *i*Pr, ciclopropilo

(53-90%)

i) $Ti(OiPr)_4$ (1.25 equiv) / *n*BuLi, de -78 ºC a t.a. ii) R^2CHO, t.a.
iii) 1) $EtAlCl_2$, 2) 3N HCl iv) 1) R^2R^3CO / $BF_3{\cdot}Et_2O$, 2) 3M HCl

Esquema II.36

Este mismo grupo desarrolló otra metodología totalmente estereoselectiva de preparación de [3]cumulenoles por acoplamiento de butadiinos con aldehídos o cetonas promovido por zirconio. La adición de los aldehídos al intermedio de zirconio cíclico **XI** ocurre únicamente en el carbono unido al sustituyente R^1 dando lugar a *cis*-2,3,4-trien-1-oles con buenos rendimientos. La adición de cetonas genera por su parte los correspondientes derivados *cis*-2,3,4-hexatrien-1,6-dioles (Esquema II.37).[64]



(75%)

XI

(35-71%)

R^1 = TMS, Pr Ph, 4-$OMeC_6H_4$, 2-tiofenilo
R^2 = Ph, Pr, 4-XC_6H_4 (X = OMe, NMe_2, NO_2), 2-tiofenilo, 2-furanilo

i) $[Cp_2ZrCl_2]$ (1.25 equiv) / EtMgBr (2.5 equiv)
ii) 1) R^2CHO, 2) H^+ iii) 1) $(Et)_2CO$, 2) H^+

Esquema II.37

64 a) Liu, Y.; Gao, H.; Zhou, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 4163. Remplazando el EtMgBr por PhLi: b) Fu, X.; Liu, Y.; Li, Y. *Organometallics* **2010**, *29*, 3012.

II.2.2. Reactividad de [3]-cumulenoles:

En la bibliografía existe un gran número de ejemplos que implican la adición intramolecular de un nucleófilo oxigenado a alenos catalizados por metales.[65] De entre ellos, son numerosos aquellos en los que los alenos involucrados presentan un grupo hidroxilo en posición α, debido a la posibilidad de estos α-alenoles de sufrir reacciones de oxiciclación por tratamiento con metales de transición, dando lugar a anillos de diferentes tamaños, con, a menudo, buen control de la regio- y estereoselectividad.[66]

En cambio, son muy escasos los ejemplos descritos hasta la fecha de reactividad de sus análogos superiores, los [3]-cumulenoles. Si bien el alto nivel de insaturación que presentan los cumulenos les convierte en compuestos con una gran y diversa reactividad, especialmente en presencia de especies metálicas,[67] el cumuleno de partida debe ser lo suficientemente estable y accesible para poder llevar a cabo transformaciones eficaces.

Entre ellos, los cumulenos tetrasustituidos que presentan un grupo hidroxilo en su estructura, los 2,3,4-trien-1-oles, cumplen estos criterios y por tanto, podrían ser excelentes materiales de partida en reacciones de oxiciclación catalizadas por metales.

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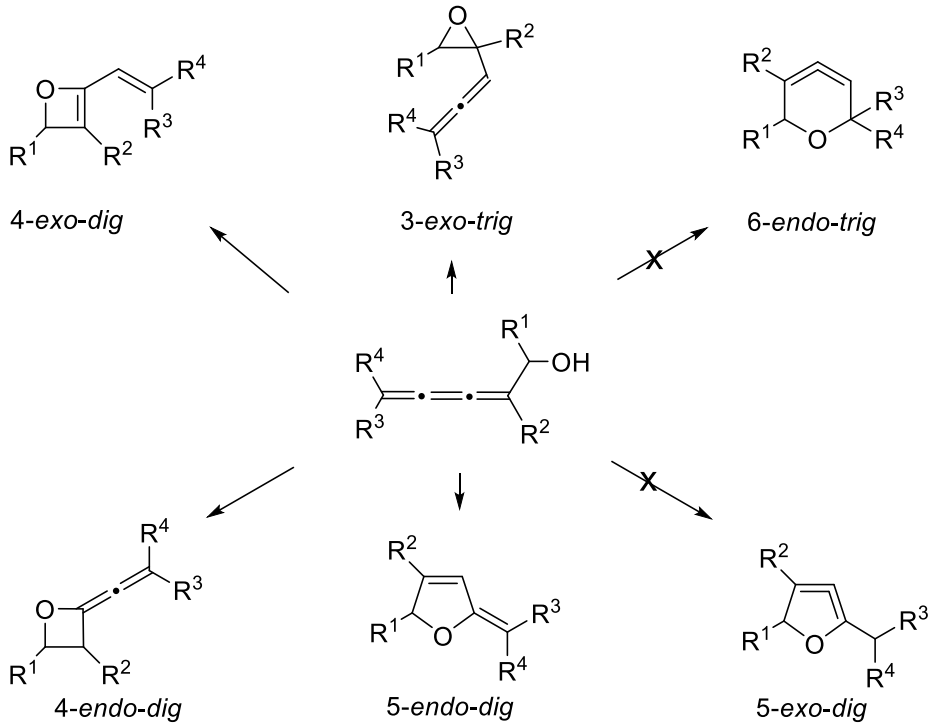
65 Para una revisión reciente de química de alenos catalizada por paladio véanse: a) referencia 14b. b) Le Bras, J.; Muzart, J. *Chem. Soc. Rev.* **2014**, *43*, 3003. Catalizada por oro véase: c) referencia 14e. Catalizada por plata y platino véase: d) Muñoz, M. P. *Chem. Soc. Rev.* **2014**, *43*, 3164.

66 Para reacciones de *O*-ciclación de α-alenoles catalizadas por oro véase: a) Alcaide, B.; Almendros, P.; Martínez del Campo, T.; Redondo, M. C.; Fernández, I. *Chem. Eur. J.* **2011**, *17*, 15005. b) Alcaide, B.; Almendros, P.; Martínez del Campo, T.; Fernández, I. *Chem. Commun.* **2011**, *47*, 9054. c) Brasholz, M.; Dugovic, B.; Reissig, H.–U. *Synthesis* **2010**, 3855. d) Gao, Z.; Li, Y.; Cooksey, J. P.; Snaddon, T. N.; Schunk, S.; Viseux, E. M. E.; McAteer, S. M.; Kocienski, P. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 5022. e) Asikainen, M.; Krause, N. *Adv. Synth. Catal.* **2009**, *351*, 2305. f) Bongers, N.; Krause, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 2178. g) Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem*. **2006**, 1387. h) Hyland, C. J. T.; Hegedus, L. S. *J. Org. Chem*. **2006**, *71*, 8658. Para reacciones de *O*-ciclación de α-alenoles catalizadas por paladio véase: i) Ma, S.; Deng, Y.; Li, J. *Chem. Eur. J*. **2008**, *14*, 4263. j) Alcaide, B.; Almendros, P.; Martínez del Campo, T. *Angew. Chem. Int. Ed*. **2006**, *45*, 4501. k) Alcaide,B. ; Almendros, P.; Rodríguez-Acebes, R. *Chem. Eur. J.* **2005**, *11*, 5708. l) Ma, S.; Gao, W. *J Org. Chem*. **2002**, *67*, 6104. m) Xu, D.; Xu, Y.; Li, L.; Ma, S. *Chem. Eur. J*. **2002**, *8*, 5012.

67 a) Furuta, T.; Asakawa, T.; Iiumina, M.; Fujii, S.; Tanaka, K.; Kan, T. *Chem. Commun*. **2006**, 3648. b) Suzuki, N.; Fukuda, Y.; Kim, C. E.; Takahara, H.; Iwasaki, M.; Saburi, M.; Nishiura, M.; Wakatsuki, Y. *Chem. Lett.* **2003**, *32*, 16. c) Suzuki, N.; Nishiura, M.; Wakatsuki, Y. *Science* **2002**, *295*, 660. d) Hashmi, S.; Polborn, K.; Szeimies, G. *Chem. Ber*. **1989**, *122*, 2399. e) Iyoda, M.; Tanaka, S.; Otani, H.; Nose, M.; Oda, M. *J. Am. Chem. Soc.* **1988**, *110*, 8494 f) Stang, P. J.; White, M. R.; Maas, G. *Organometallics* **1983**, *2*, 720.

Así, las reacciones de *O*-ciclación intramolecular de estos α-cumulenoles podrían dar lugar a diferentes oxaciclos de 3, 4, 5 ó 6 eslabones, dependiendo de la regioselectividad del proceso. De los seis aductos de cicloisomerización posibles, los procedentes de un ataque *5-exo-dig* o *6-endo-trig*, alenos cíclicos, no se formarían debido su gran rigidez estructural (Esquema II.38).

Sin embargo, a pesar de esta interesante potencial reactividad, en la literatura no existen apenas ejemplos de reacciones de 2,3,4-trien-1-oles.[68]

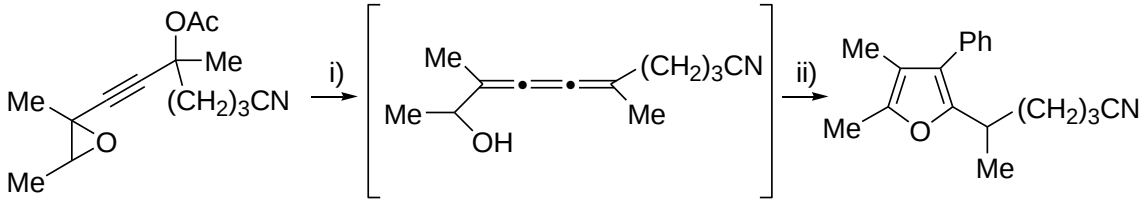


Esquema II.38

El único ejemplo descrito hasta la fecha de reacciones de oxiciclación de 2,3,4-trien-1-oles fue llevado a cabo por Aurrecoechea y col. en el año 2001. Los autores desarrollaron un método de síntesis de furanos tri y tetrasustituidos a partir de [3]cumulenoles, generados *in situ* y sin llegar a ser aislados en la mayoría de los

68 Una vez comenzada nuestra investigación, el grupo de Fensterbank describió una síntesis de furanos y dieninos catalizada por oro a partir de [3]-cumulenoles: a) Ferrand, L.; Das Neves, N.; Malacria, M.; Mouriès-Mansuy, V.; Ollivier, C.; Fensterbank, L. *J. Organomet. Chem.* **2015**, *795*, 53. Para la síntesis de 1,5-dien-3-inos por reacción de deshidratación de [3]-cumulenoles, véase: b) Wang, E.; Fu, X.; Xie, X.; Chen, J.; Gao, H.; Liu, Y. *Tetrahedron Lett*. **2011**, *52*, 1968

casos, a partir de 4,5-epoxi-2-alquinil-ésteres mediante catálisis de paladio (Esquema II.39). [69]



(56%)

i) 1) SmI_2(2.5 equiv), THF 2) H_2O

ii) $Pd(PPh_3)_4$ (5 mol%), Et_3N, PhI, DMF, 70 ºC

Esquema II.39

II.3. El núcleo β-lactámico como sintón en Química Orgánica

Los sistemas β-lactámicos son ampliamente conocidos y estudiados debido a sus propiedades antibacterianas y constituyen, junto con los macrólidos y las fluoroquinolonas, una de las tres clases más importantes de antibióticos. La actividad antibacteriana de las β-lactamas se debe a su capacidad para inhibir enzimas esenciales en la síntesis de la pared bacteriana, de modo que ésta o bien no se forma o bien no lo hace correctamente, lo que, en cualquier caso lleva a la muerte celular.[70]

La reactividad y selectividad de estos compuestos frente a diferentes sustratos biológicos depende tanto de los sustituyentes del ciclo de cuatro eslabones como de los anillos fusionados a él. Sin embargo, los microorganismos han desarrollado diferentes estrategias para defenderse de la acción antibiótica como por ejemplo, la síntesis de enzimas denominadas genéricamente β-lactamasas, que destruyen el anillo de 2- azetidinona por hidrólisis o derivatización

69 Véase referencia 61.

70 a) Hubschwerlen, C. *β-Lactam Antibiotics. Comprehensive Medicinal Chemistry II,* Vol. 7; Taylor, J. B.; Triglle, D., Eds.; Elsevier Ltd: Oxford, UK, 2007, 479. b) Page, M. I.; Laws, A. P. *Tetrahedron* **2000**, *56*, 5631. c) Neu, H. C. *The Chemistry of β-lactams*; Page, M. I., Ed.; Blackie: Glasgow, 1992, 101. d) Frère, J. M.; Nguyen-Distèche, M.; Coyette, J.; Joris, B. *The Chemistry of β-lactams*; Page, M. I., Ed.; Blackie: Glasgow, 1992, 148. e) Herzberg, O.; Moult, J. *Curr. Opi. Struct. Biol.* **1991**, *1*, 946. f) *Chemistry and Biology of β-Lactam Antibiotics,* Vol. 1*;* Morin, R. B.; Gorman, M., Eds.; Academic Press: New York, 1982.

(acetilación, fosforilación, nucleotidación) del mismo.[71] La rápida evolución de la resistencia bacteriana frente a los antibióticos β-lactámicos ha impulsado la investigación en busca de nuevos compuestos más eficaces.[72]

Además, en los últimos años se han descubierto nuevos derivados de β-lactamas que presentan una importante actividad biológica como inhibidores enzimáticos, por ejemplo el ezetimibe (inhibidor del colesterol),[73] los inhibidores de proteasas, trombina y del antígeno específico de la próstata,[74] y con actividad anticancerígena y antimalárica.[75]

Sin embargo, la importancia del núcleo de 2-azetidinona no se limita únicamente a su actividad farmacológica, su utilidad como intermedio sintético también le confiere un gran valor en el campo de la Síntesis Orgánica. La elevada tensión anular del anillo de 2-azetidinona determina que la ruptura por cualquiera de los cuatro enlaces sencillos que la conforman resulte fácilmente inducible, haciendo de este núcleo un intermedio sintético muy versátil y de gran aplicabilidad.[76]

El desarrollo de esta metodología sintética basada en el núcleo de 2-azetidinona, denominada "método del sintón β-lactámico",[77] ha sido objeto de numerosas investigaciones debido a su importancia en la preparación estereocontrolada de productos nitrogenados de interés biológico.[78]

Si bien la ruptura del enlace N1–C2 es la más frecuente e importante desde el punto de vista biológico, al estar implicada en la actividad antibacteriana de

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71 Fisher, J. F.; Meroueh, S. O.; Mobashery, S. *Chem. Rev.* **2005**, *105*, 395.

72 a) Singh, G. S. *Mini-Rev. in Med. Chem.* **2004**, *4*, 69. b) Singh, G. S. *Mini-Rev. in Med. Chem.* **2004**, *4*, 93. c) Dalhoff, A.; Thomson, C. J. *Chemotherapy* **2003**, *49*, 105.

73 a) Kvœrnø, L.; Werder, M.; Hauser, H.; Carreira, E. M. *J. Med. Chem.* **2005**, *48*, 6035. b) Kvœrnø, L.; Ritter, T.; Werder, M.; Hauser, H.; Carreira, E. M. *Angew. Chem. Int. Ed*. **2004**, *43*, 4653. c) Clader, J. W. *J. Med. Chem.* **2004**, *47*, 1.

74 a) Corey, E. J.; Hogan, P. C. *J. Am. Chem. Soc.* **2005**, *127*, 15386. b) Gerona-Navarro, G.; Pérez de Vega, M. J.; García-López, M. T.; Andrei, G.; Snoeck, R.; Balzarini, J.; De Clercq, E.; González-Muñiz, R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2253. c) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Maggioni, F.; Puglisi, A. *J. Org. Chem.* **2003**, *68*, 2952. d) Adlington, R. M.; Baldwin, J. E.; Becker, G. W.; Chen, B.; Cheng, L.; Cooper, S. L.; Hermann, R. B.; Howe, T. J.; McCoull, W.; McNulty, A. M.; Neubauer, B. L.; Pritchard, G. J. *J. Med. Chem.* **2001**, *44*, 1491.

75 a) *Heterocyclic Scaffolds I: β-Lactams.* **2010**, *22*, 379; en *Topics in Heterocyclic Chemistry*; Banik, B. K., Ed.; Springer: Berlin, 2010. b) Avilés, E.; Rodríguez, A. D. *Org. Lett.* **2010**, *12*, 5290. c) Banik, B. K.; Becker, F. F.; Banik, I. *Bioorg. Med. Chem.* **2004**, *12*, 2523. d) Banik, I.; Becker, F. F.; Banik, B. K. *J. Med. Chem.* **2003**, *46*, 12.

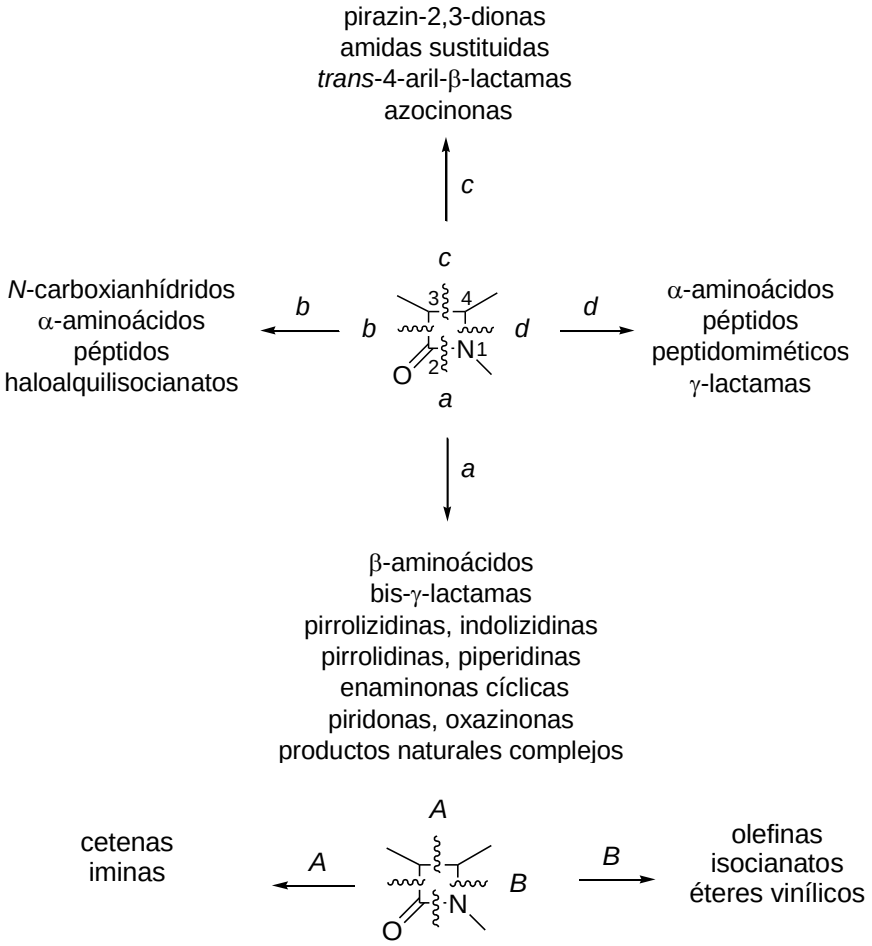
76 Véase referencia 7.

77 Véanse referencias 7h y 7i.

78 Véanse referencias 7c y 7d.

estas moléculas,[79] se conocen ejemplos de ruptura selectiva de los restantes enlaces del anillo β-lactámico.

Las distintas posibilidades de apertura del núcleo de β-lactama, junto con algunos de los diferentes tipos de productos originados, se recogen en el Esquema II.40.



Esquema II.40

II.3.1. Ruptura del enlace N1–C2:

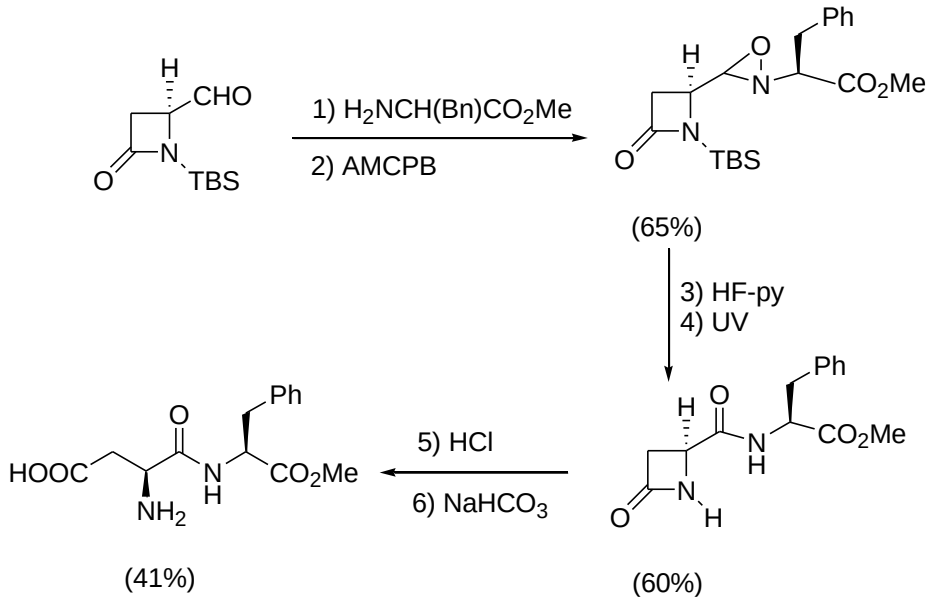
Desde el primer ejemplo descrito por Bose,[80] la ruptura del enlace amídico ha sido objeto de numerosas investigaciones. Este proceso ocurre

[79] Beardsell, M.; Hinchliffe, P. S.; Wood, J. M.; Wilmouth, R. C.; Schofield, C. J.; Page, M. I. P. *Chem. Commun.* **2001**, 497.

[80] Manhas, M. S.; Amin, S. G.; Bose, A. K. *Heterocycles* **1976**, *5*, 669.

fundamentalmente, por el ataque de un agente nucleófilo al carbono carbonílico, incluso de una molécula de agua. Por ello, las β-lactamas pueden ser consideradas como formas cíclicas de β-aminoácidos, donde el grupo ácido y amino se encuentran protegidos simultáneamente. Por lo tanto, la aplicación más directa de este tipo de apertura del anillo de 2-azetidinona es la síntesis de β-aminoácidos. Además, la rigidez inherente al núcleo β-lactámico hace que esta metodología sea con frecuencia altamente estereoselectiva.

Un ejemplo interesante es la síntesis del dipéptido aspartamo a partir de un compuesto β-lactámico, donde la secuencia de reacciones para dar lugar al producto deseado se completa con una hidrólisis ácida del enlace N1–C2 (Esquema II.41).[81]

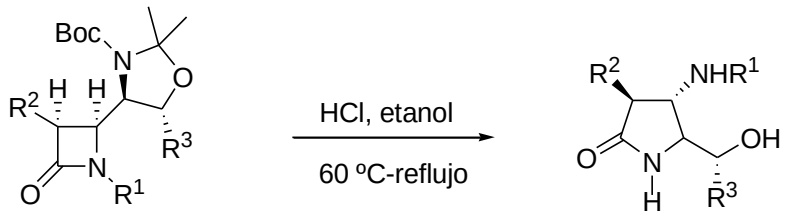


Esquema II.41

El núcleo de β-lactama también resulta un precursor adecuado para la obtención de pirrolidin-2-onas densamente sustituidas. Un ejemplo lo constituye la transformación de 4-(α-aminoalquil)-β-lactamas derivadas del aldehído de Garner en 3,5-dialquil-4-aminopirrolidinonas, por hidrólisis del aminoacetal en medio ácido y posterior reagrupamiento al anillo de cinco miembros (Esquema II.42).[82]

81 Duhamel, P.; Goument, P.; Plaquevent, J. C. *Tetrahedron Lett.* **1987**, *28*, 2595.

82 a) Shindo, M.; Ohtsuki, K..; Shishido, K. *Tetrahedron: Asymmetry* **2005**, *16*, 2821. b) Jayaraman, M.; Puranik, V. G.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 9005. c) Palomo, C.; Cossío, F. P.; Cuevas, C.; Odriozola, J. M.; Ontoria, J. M. *Tetrahedron Lett.* **1992**, *33*, 482. 482. d) Para la

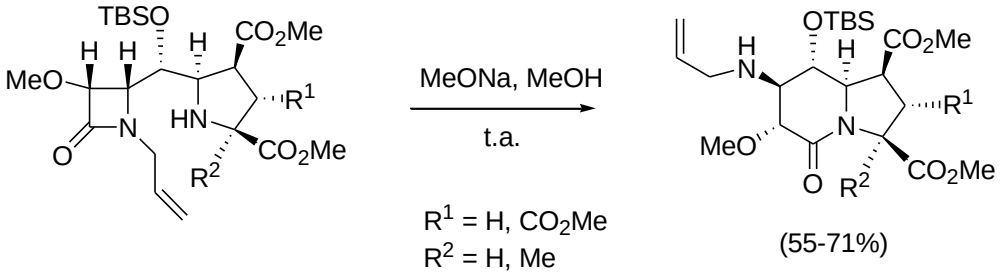


R^1 = PMP, Bn; R^2 = H, Et; R^3 = H, Me (80-90%)

R^1 = PMP, Bn; R^2 = OMe, OBn, OPh; R^3 = Ph (97-99%)

Esquema II.42

En nuestro grupo de investigación, por su parte, se ha llevado a cabo la síntesis estereocontrolada de indolizidinonas polifuncionalizadas, a través de un proceso secuencial de cicloadición 1,3-dipolar catalizada por $AgNO_3$ de iminas derivadas de 4-(1-alcoxi-2-formil)-β-lactamas y α-aminoésteres, seguido de reagrupamiento por tratamiento con metóxido sódico en metanol a temperatura ambiente (Esquema II.43).[83]



R^1 = H, CO_2Me

R^2 = H, Me

(55-71%)

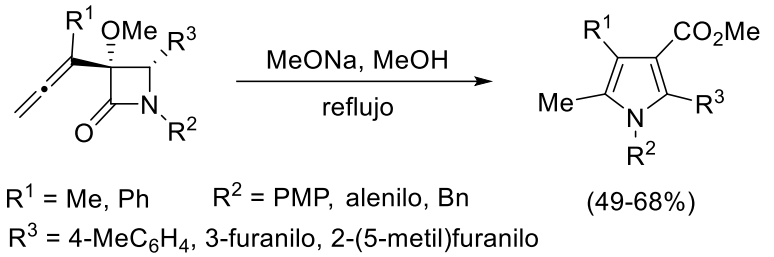
Esquema II.43

Utilizando una metodología análoga y (α-alcoxialenil)-β-lactamas como materiales de partida, se describió una síntesis directa de pirroles polisustituidos sin necesidad de utilizar metales de transición (Esquema II.44).[84] Esta reacción puede explicarse a través de un proceso dominó que implica, en primer lugar, la apertura del anillo de 2-azetidinona, seguido de aminociclación con el grupo alénico y aromatización del anillo formado.

síntesis de γ-lactamas a partir de 2-azetidinonas que poseen un grupo iminofosforano véase: Alcaide, B.; Almendros, P.; Alonso, J. M. *J. Org. Chem*. **2004**, *69*, 993.

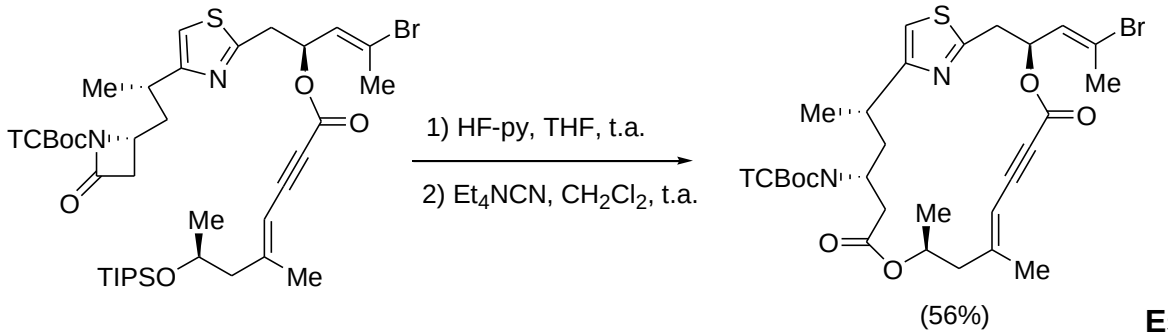
83 a) Alcaide, B.; Almendros, P.; Redondo, M. C.; Ruiz, M. P. *J. Org. Chem*. **2005**, *70*, 8890. Para la síntesis de piperidin-2-onas a partir de 4-oxoazetidin-2-carbaldehídos véase: b) Krishnaswamy, D.; Govande, V. V.; Deshmukh, A. R. A. S. *Synthesis* **2003**, 1903.

84 a) Alcaide, B.; Almendros, P.; Carrascosa, R.; Redondo, M. C. *Chem. Eur. J.* **2008**, *14*, 637. b) Alcaide, B.; Almendros, P.; Redondo, M. C. *Chem Commun.* **2006**, 2616.



Esquema II.44

Otro ejemplo de la versatilidad de la ruptura del enlace N1–C2 a la hora de acceder a compuestos de elevado interés biológico fue descrito por Romo y col. para la preparación de derivados de Pateamina A, producto natural que actúa como inmunodepresor. Una de las etapas clave en la preparación de estos compuestos implica este tipo de ruptura del núcleo β-lactámico presente en el precursor de macrociclación, tal y como se muestra en el Esquema II.45.[85]



Esquema II.45

Por otro lado, Buchwald y col. describieron un método sencillo para la preparación de anillos nitrogenados de tamaño medio a través de un proceso tándem catalizado por cobre. En primer lugar se produce el acoplamiento entre una NH-β-lactama y un bromuro o yoduro de arilo, seguido de una transamidación intramolecular que implica, la ruptura del enlace N1–C2 del anillo β-lactámico y la consiguiente expansión de anillo (Esquema II.46). [86]

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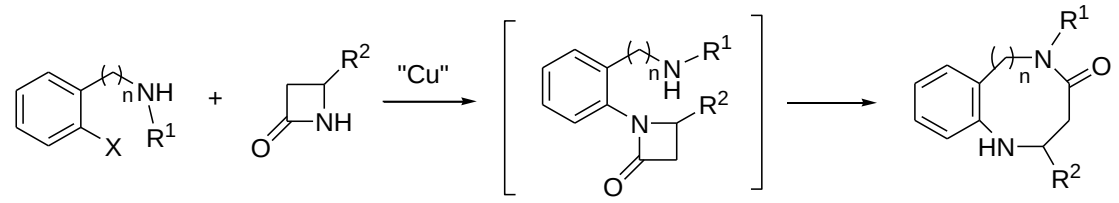
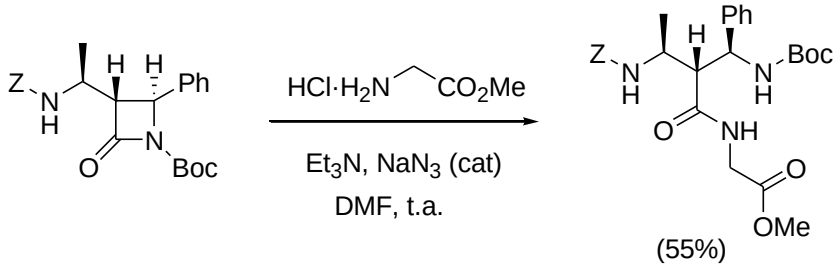
85 a) Romo, D.; Choi, N. S.; Li, S.; Buchler, I.; Shi, Z.; Liu, J. O. *J. Am. Chem. Soc*. **2004**, *126*, 10582. Para otros ejemplos de síntesis de derivados de productos naturales véanse: b) Chen, A.; Nelson, A.; Tanikkul, N.; Thomas, E. J. *Tetrahedron Lett.* **2001**, *42*, 1251. c) Eggen, M. J.; Nair, S. V.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1813. d) Wasserman, H. H.; Leadbetter, M. R. *Tetrahedron Lett.* **1985**, *26*, 2241. e) Wasserman, H. H.; Matsuyama, H. *J. Am. Chem. Soc.* **1981**, *103*, 461.

86 Buchwald, S. L.; Klapars, A.; Parris, S.; Anderson, K. W. *J. Am. Chem. Soc.* **2004**, *126*, 3529.



Esquema II.46

El grupo de Podlech fue el primero en describir la síntesis de peptidomiméticos formados por β,β´-aminoácidos utilizando β-lactamas. El ataque nucleófilo de un aminoéster en presencia de cantidades catalíticas de azida sódica provoca la ruptura del enlace N1–C2 del anillo de β-lactama, pudiéndose obtener de forma sencilla y eficaz el peptidomimético que se muestra en el Esquema II.47 a partir del éster metílico de glicina y la 2-azetidinona correspondiente.[87]

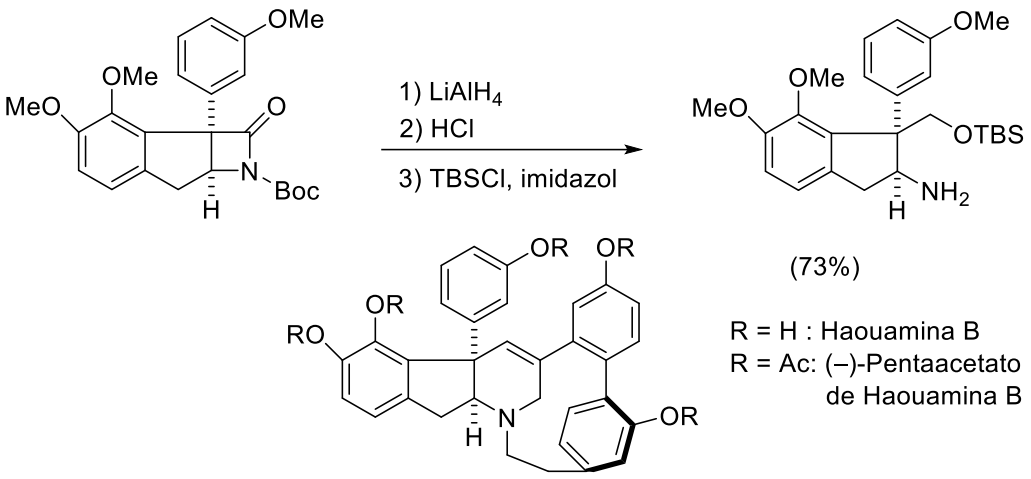


Esquema II.47

Por su parte, Tokuyama y col. emplearon esta ruptura del anillo β-lactámico para llevar a cabo la primera síntesis total enantioselectiva del pentaacetato de Haouamina B, un producto natural con alta actividad citotóxica. La ruta implica la ruptura del enlace N1–C2 de la β-lactama, mediante una reducción de ésta con $LiAlH_4$ (Esquema II.48).[88]

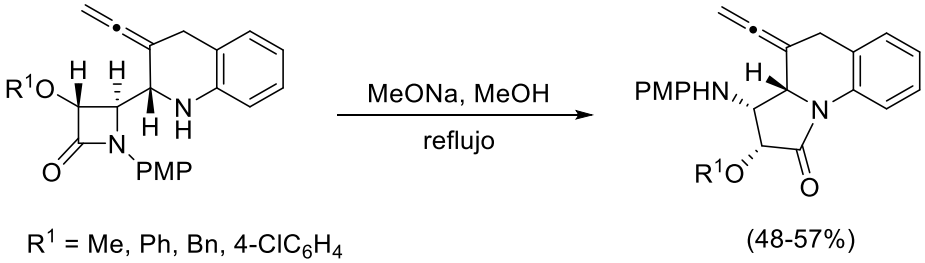
87 a) Taubinger, A. A.; Fenske, D.; Podlech, J. *Synlett* **2008**, 539. Para compuestos similares a partir de 3-beniciloxi-β-lactamas véanse: b) Palomo, C.; Aizpurua, J. M.; Cuevas, C.; Mielgo, A.; Galarza, R. *Tetrahedron Lett.* **1995**, *36*, 9027. c) Palomo, C.; Aizpurua, J. M.; Cuevas, C. J. *Chem. Soc., Chem. Commun.* **1994**, 1957.

88 Momoi, Y.; Okuyama, K.; Toya, H.; Sugimoto, K.; Okano, K.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2014**, *53*, 13215.



Esquema II.48

Recientemente, en nuestro grupo de investigación se ha descrito la síntesis de indolizidinonas unidas a β-aminoalenos mediante la ruptura del enlace N1–C2 de β-lactamas con un sustituyente aminoalénico en su estructura, a través de un reordenamiento quimioselectivo promovido por metóxido sódico en metanol (Esquema II.49).[89]



Esquema II.49

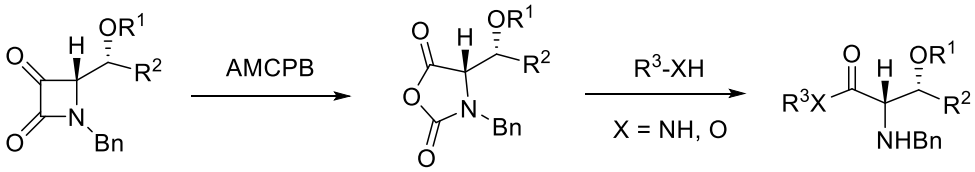
II.3.2. Ruptura del enlace C2–C3:

El primer ejemplo descrito de ruptura del enlace C2–C3 del anillo β-lactámico se llevó a cabo en *N*-halo-2-azetidinonas para dar lugar a haloalquilisocianatos.[90] Posteriormente, Palomo y col. describieron una nueva síntesis de α-aminoácidos a partir de azetidin-2,3-dionas. Este procedimiento

89 a) Alcaide, B.; Almendros, P.; Martín- Montero, R.; Ruiz, M. P. *Adv. Synth. Catal.* **2016**, *358*, 1469. b) Alcaide, B.; Almendros, P.; Fernández, I.; Martín- Montero, R.; F. Martínez-Peña, F.; Ruiz, M. P.; Torres, M. R. *ACS Catal.* **2015**, *5*, 4842.

90 Kampe, K.–D. *Tetrahedron Lett.* **1969**, *10*, 117.

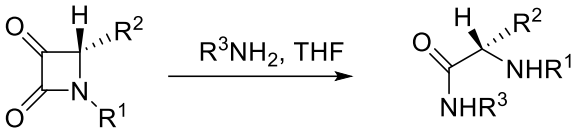
consta de una oxidación de Baeyer–Villiger para generar *N*-carboxianhídridos, que se acoplan con aminas o alcoholes obteniéndose los derivados de α-aminoácidos con buenos rendimientos (Esquema II.50).[91]



R^1 = TBS, TBDPS (90-95%) (70-80%)
R^2 = *i*Pr, *i*Bu, Bn
R^3 = (*S*)-CH(CH_2Ph)CO_2Bn, (*S*)-CH(CH_2CH(CH_3)$_2$)CO_2Bn, (*S*)-CH(CH_2CH(CH_3)$_2$)CO_2Bn

Esquema II.50

En nuestro grupo se ha diseñado una estrategia diferente para la preparación de α-aminoácidos a partir de azetidin-2,3-dionas, que también implica la ruptura del enlace C2–C3. La reacción de estos sustratos, tanto en su forma racémica como en su variante ópticamente pura, con una amplia variedad de aminas primarias y secundarias, proporciona a través de una única etapa sintética las correspondientes α-aminoamidas (Esquema II.51).[92] Este proceso resulta especialmente interesante en la reacción con α-aminoésteres, ya que proporciona péptidos ópticamente puros de una forma rápida y sencilla.



(45–77%)

R^1 = PMP, alilo
R^2 = Ph, 2,2-dimetil-[1,3]dioxolan-4-ilo
R^3 = Bn, alilo, propargilo

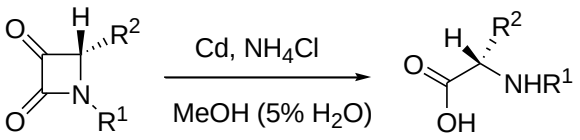
Esquema II.51

Esta metodología se extendió posteriormente a nucleófilos oxigenados. Así, el tratamiento de azetidin-2,3-dionas con Cd/NH_4Cl en metanol acuoso (5% de

91 a) Palomo, C; Aizpurua, J.M.; Ganboa, I.; Oiarbide, M. *Amino-acids*, **1999**, *16*, 321; b) Cossío, F. P.; López, C.; Oiarbide, M.; Palomo, C.; Aparicio, D.; Rubiales, G. *Tetrahedron Lett.* **1988**, *29*, 3133. Para otra síntesis de aa con ruptura del enlace C2–C3, véase: Palomo, C.; Oiarbide, M.; Landa, A.; Esnal, A.; Linden, A. *J. Org. Chem.* **2001**, *66*, 4180.

92 Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Commun.* **2000**, 757.

agua), dio lugar a los correspondientes α-aminoácidos con rendimientos moderados. (Esquema II.52).[93]

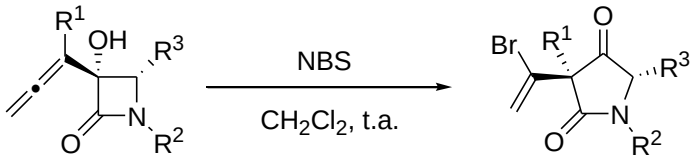


(45-58%)

R^1 = Bn, PMP, 2-propinilo
R^2 = Ph, 2,2-dimetil-[1,3]dioxolan-4-ilo

Esquema II.52

Recientemente, nuestro grupo de investigación ha descrito una ruptura selectiva del enlace C2–C3, que supone una expansión del anillo de 2-azetidinona para formar pirrolidin-2,4-dionas (ácidos tetrámicos). Desde alenoles β-lactámicos y por tratamiento con *N*-bromosuccinimida, tiene lugar el reagrupamiento de forma quimio-, regio- y diastereoselectiva (Esquema II.53).[94]



(40-96%)

R^1 = Me, Ph, PMP R^2 = Bn, PMP
R^3 = 4-MeC_6H_4 2,2-dimetil-[1,3]dioxolan-4-ilo, β-lactama

Esquema II.53

II.3.3. Ruptura del enlace C3–C4:

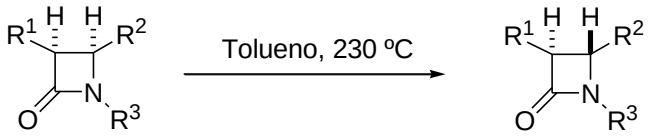
La ruptura del enlace C3–C4 del anillo β-lactámico se describió por primera vez en 3,3-difenil-4-amino-β-lactamas, mediante la formación de carbaniones intermedios, para dar lugar a diferentes amidas sustituidas.[95]

93 Alcaide, B.; Almendros, P; Aragoncillo, *Chem. Eur. J.* **2002**, *8*, 3646.

94 a) Alcaide, B.; Almendros, P.; Luna, A.; Cembellín, S.; Arnó, M.; Domingo, L. R. *Chem. Eur. J*. **2011**, *17*, 11559. b) Alcaide, B.; Almendros, P.; Luna, A.; Torres, M. R. *Adv. Synth. Catal*. **2010**, *352*, 621.

95 a) Bose, A. K.; Kugajevsky, I. *Tetrahedron* **1967**, *23*, 957. Para la primera ruptura C3-C4 a través de carbocationes véase: b) Alcaide, B.; Martín-Cantalejo, Y.; Rodríguez-López, J.; Sierra, M. A. *J. Org. Chem.* **1993**, *58*, 4767.

Posteriormente, en nuestro grupo de investigación se descubrió un método eficaz para la isomerización *cis*/*trans* de 4-aril-β-lactamas por calefacción en tolueno a 230°C. Este proceso es el primer ejemplo descrito de isomerización térmica en β-lactamas (Esquema II.54).[96] La reacción debe transcurrir por ruptura homolítica del enlace C3–C4, seguido de rotación de enlace y posterior ciclación, para dar el producto termodinámicamente más estable, la *trans*-2-azetidinona.



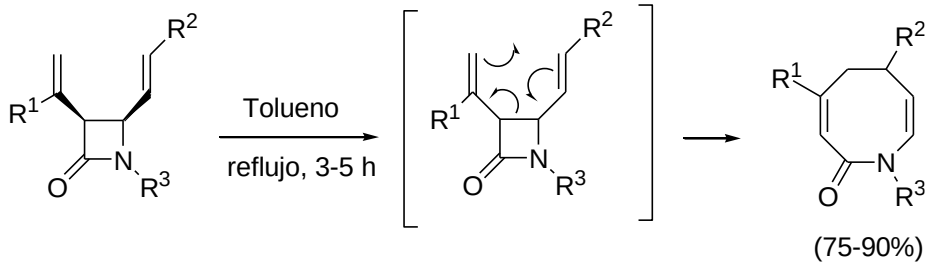
cis–β-lactama → *trans*–β-lactama (44-67%)

R^1 = OMe, OPh

R^2 = PMP, 2-furilo, 3-furilo, 3-tienilo R^3 = Bn, alilo, propargilo, 3-butenilo

Esquema II.54

Asimismo, nuestro grupo describió la síntesis estereoselectiva de tetrahidroazocinonas, tanto en forma racémica como óptimamente pura, a partir de dialquenil-β-lactamas. Como se muestra en el Esquema II.52, se trata de un proceso de reagrupamiento sigmatrópico [3,3] inducido térmicamente (transposición de Cope), en el que se produce la ruptura del enlace C3–C4 β-lactámico.[97]



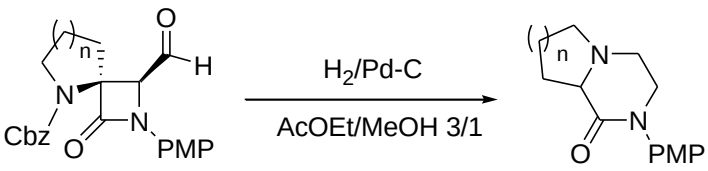
(75-90%)

R^1 = H, Me ; R^2 = CO_2Me, Ph; R^3 = PMP, Bn, (*R*)-CH(Me)Ph

Esquema II.55

[96] Alcaide, B.; Almendros, P.; Salgado, N. R.; Rodríguez-Vicente, A. *J. Org. Chem.* **2000**, *65,* 4453.
[97] Alcaide, B.; Rodríguez-Ranera, C.; Rodríguez-Vicente, A. *Tetrahedron Lett*. **2001**, *42*, 3081.

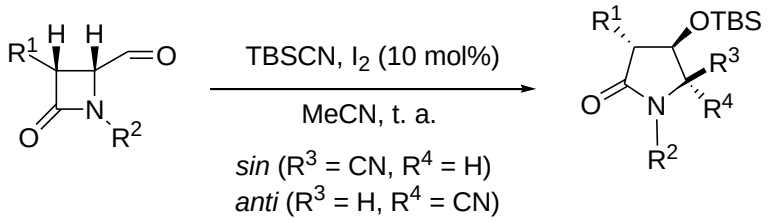
González y col. por su parte desarrollaron un procedimiento de obtención de sistemas diazabicíclicos mediante hidrogenolisis de espiro β-lactamas, con ruptura del enlace C3–C4 y posterior reordenamiento, dando lugar a piperazinas bicíclicas con excelentes rendimientos (Esquema II.56).[98]



n = 1 (90%) n = 2 (92%)

Esquema II.56

En nuestro grupo de trabajo se describió una nueva ruptura del enlace C3–C4 del anillo de β-lactama que permite la preparación diastereoselectiva de 5-ciano-3,4-dihidroxipirrolidin-2-onas ópticamente puras por catálisis con yodo molecular en presencia de cianuro de *t*-butildimetilsililo (Esquema II.57).[99]



R^1 = MeO, BnO
R^2 = PMP, Bn, alilo

(62-78%)
sin/anti: 100/0- 86/14

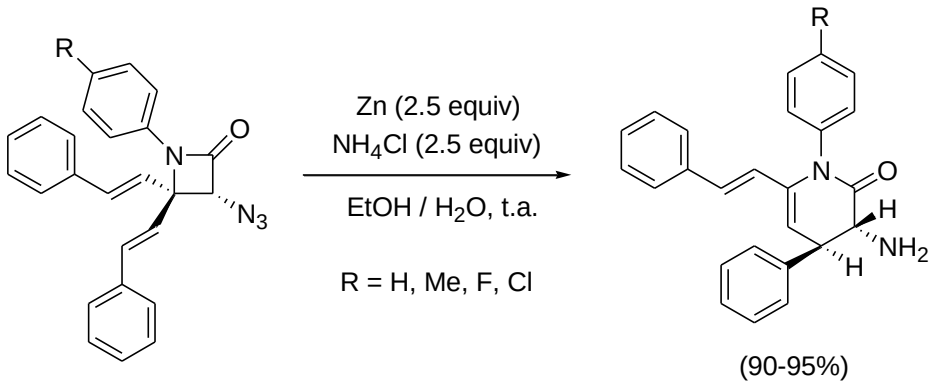
Esquema II.57

El grupo de Mahajan llevó a cabo la preparación estereoselectiva de 2-piridonas mediante la ruptura del enlace C3–C4 del anillo β-lactámico de 2-azetidinonas diferentemente sustituidas en la posición C3, en un solo paso y utilizando condiciones suaves de reacción (Esquema II.58).[100]

98 Macías, A.; Alonso, E.; del Pozo, C.; González, J. *Tetrahedron Lett*. **2004**, *45*, 4657.

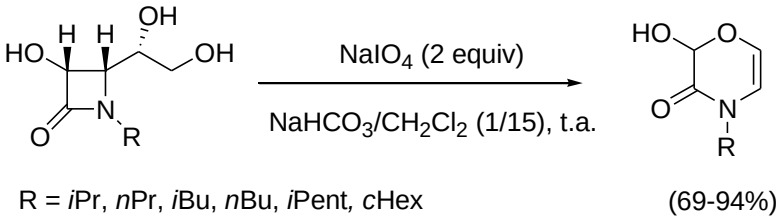
99 a) Alcaide, B.; Almendros, P.; Cabrero, G.; Callejo, R.; Ruiz, M. P.; Arnó, M.; Domingo, L. R. *Adv. Synth. Catal.* **2010**, *352,* 1688. b) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Chem. Commun*. **2008**, 615.

100 Singh, P.; Singh, P.; Kumar, K.; Kumar, V.; Mahajan,M. P.; Bisetty, K. *Heterocycles* **2012**, *86*, 1301.



Esquema II.58

Por otro lado, De Kimpe, Van Speybroeck y col. describieron la síntesis de 2-hidroxi-1,4-oxazin-3-onas utilizando β-lactamas como materiales de partida, mediante una inesperada ruptura del enlace C3–C4 β-lactámico seguida de una expansión del anillo (Esquema II.59).[101]



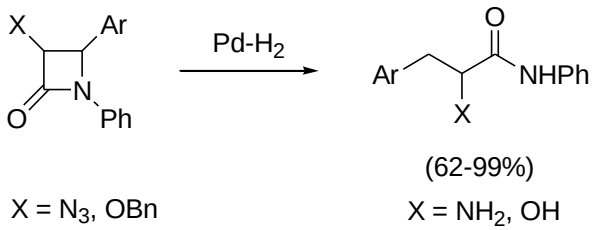
Esquema II.59

II.3.4. Ruptura del enlace N1–C4:

Ojima y col. fueron los primeros en describir un procedimiento de ruptura del enlace N1–C4, en una reacción de hidrogenolisis de 4-aril-2-azetidinonas catalizada por paladio (Esquema II.60).[102] Este descubrimiento fue el que permitió desarrollar la metodología del sintón β-lactámico, pudiéndose sintetizar α-aminoácidos, α-hidroxiácidos, dipéptidos, oligopéptidos, peptidomiméticos, taxoides, poliamidas y poliaminoalcoholes.

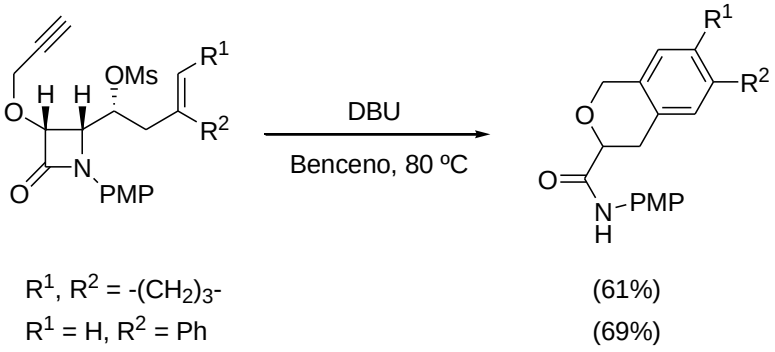
101 Mollet, K.; Goossens, H.; Piens, N.; Catak,S.; Waroquier, M.; Törnroos, K. W.; Van Speybroeck, V.; D´hooghe, M.; De Kimpe, N. *Chem. Eur. J.* **2013**, *19*, 3383.

102 a) Ojima, I.; Qiu, X. *J. Am. Chem. Soc.* **1987**, *109*, 6537. b) Ojima, I.; Suga, S.; Abe, R. *Chem. Lett.* **1980**, 853.



Esquema II.60

Empleando esta nueva ruptura, en nuestro grupo de investigación se estudió el tratamiento de mesilatos derivados de enino-β-lactamas enantioméricamente puras con un ligero exceso de DBU para dar lugar a isocromanos racémicos (Esquema II.61).[103] El mecanismo propuesto para la formación de estos productos supone la ruptura del enlace N1–C4 seguida de una ciclación Diels–Alder intramolecular.



Esquema II.61

La ruptura del enlace N1–C4 β-lactámico se aplicó posteriormente a la síntesis de γ-lactamas a partir de *N*-bencil-4-fenil-2-azetidinonas en presencia de una base. Es de resaltar que la reacción procede con total diaestereoselectividad a favor del isoméro *anti*. La presencia de un grupo fenilo en posición C4 del anillo β-lactámico es condición necesaria para que la expansión tenga lugar, puesto que este grupo estabiliza el carbanión generado (Esquema II.62).[104]

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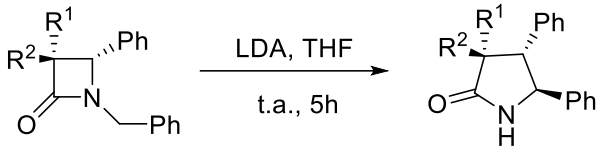
103 Alcaide, B.; Almendros, P.; Pardo, C.; Rodríguez-Ranera, C.; Rodríguez-Vicente, A. *J. Org. Chem.* **2003**, *68*, 3106.

104 a) Park, J.–H.; Ha, J.–R.; Oh, S.–J.; Kim, J.–A.; Shin, D.-S.; Won, T.–J.; Lam, Y.–F.; Ahn, C. *Tetrahedron Lett.* **2005**, *46*, 1755. b) Escalante, J.; González-Tototzin, M. A. *Tetrahedron: Asymmetry* **2003**, *14*, 981.

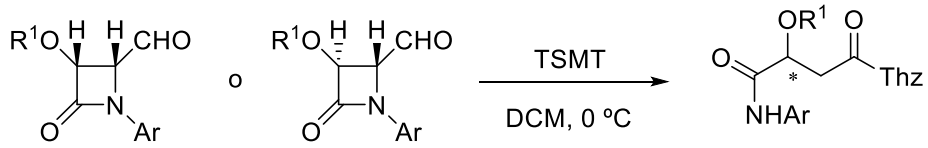


R^1= Me, Ph
R^2= Me, Ph

(65-67%)

Esquema II.62

Nuestro grupo de investigación fue el primero en describir la ruptura del enlace N1–C4 en un núcleo de 2-azetidinona que no presentaba un sustituyente aromático en la posición C4. La adición de 2-(trimetilsili)tiazol tanto a *cis* como a *trans* 4-formil-β-lactamas condujo a la formación de derivados de α-alcoxi-γ-cetoácidos enantiopuros (Esquema II.63).[105]

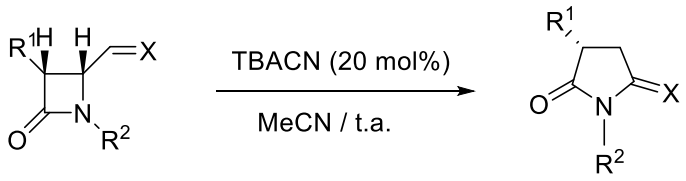


R^1 = Me, Bn
Ar = 4-YC_6H_4 (Y = OMe, Me, NMe_2, Br), 2,4-$OMeC_6H_4$

(*R*) o (*S*)
(33-58%)

Esquema II.63

También se estudió la expansión del anillo β-lactámico para obtener 5-imino-pirrolidin-2-onas y succinimidas a través de una ruptura N1–C4 de las correspondientes 4-imino-β-lactamas y 4-oxoazetidin-2-carbaldehídos mediante catálisis con cianuro de tetrabutilamonio (Esquema II.64).[106]



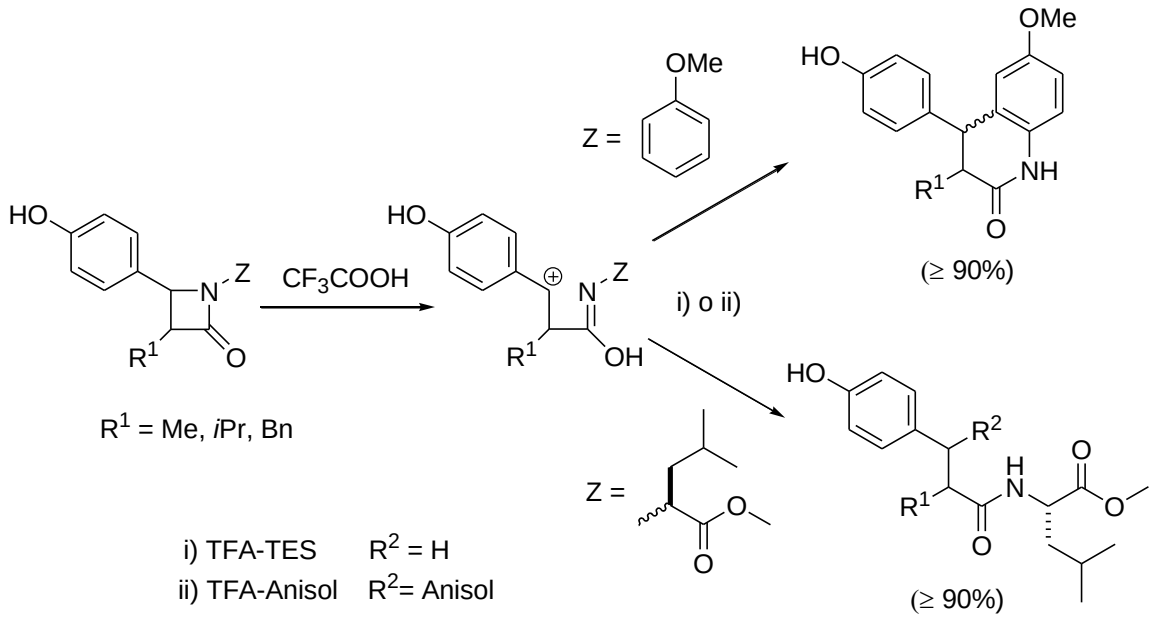
X = O, R^1 = OMe, OBn, R^2 = PMP (50-55%)
X = NR^3, R^1 = OMe, OBn, R^2 = PMP, Bn, alilo (44-70%)
R^3 = 4-YC_6H_4 (Y = OMe, Me, NMe_2, Cl)

Esquema II.64

105 Alcaide, B.; Almendros, P.; Redondo, M. C.. *Org. Lett.* **2004**, 6, 1765.

106 a) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Org. Lett.* **2005**, *7*, 3981. Para la síntesis de succinimidas enantiopuras catalizada por sales de tiazolio: b) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Chem. Commun*. **2007**, 4788.

Por otro lado, McMurray y col. describieron la ruptura del enlace β-lactámico N1–C4 en condiciones ácidas para dar lugar a un carbocatión intermedio bencílico, el cual puede reducirse con silanos o participar en reacciones de Fridedel-Crafts inter o intramoleculares, dando lugar a análogos de tirosina (Esquema II.65).[107]

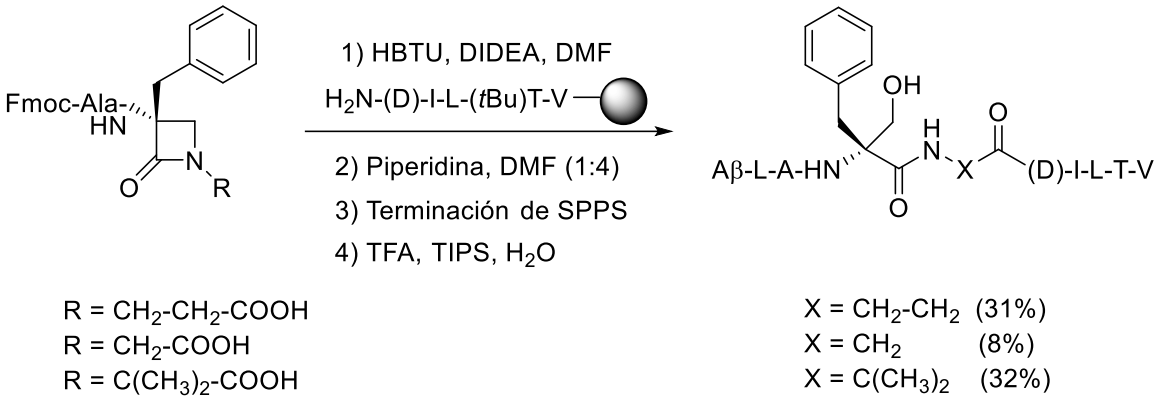


Esquema II.65

El grupo de Quideau por su parte describió la ruptura del enlace N1–C4 en β-lactamas no sustituidas en la posición C4, a través de un ataque nucleófilo vía SN_2 de una molécula de agua durante su estudio de síntesis de híbridos peptídicos β-lactámicos (Esquema II.66).[108]

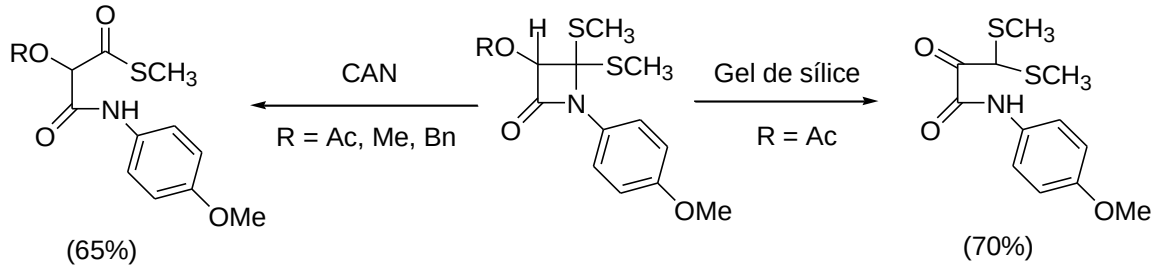
107 a) Mandal, P. K.; Cabell, L. A.; McMurray, J. S. *Tetrahedron Lett.* **2005**, *46*, 3715. Para la ruptura del enlace N1-C4 en condiciones básicas véase: b) Cabell, L. A.; McMurray, J. S. *Tetrahedron Lett*. **2002**, *43*, 2491. c) Cabell, L. A.; Hedrich, L. W.; McMurray, J. S. *Tetrahedron Lett*. **2001**, *42*, 8409.

108 Tarbe, M.; Azcune, I.; Balentová, E.; Miles, J. J.; Edwards, E. E.; Miles, K. M.; Do, P.; Baker, B. M.; Sewell, A. K.; Aizpurua, J. M.; Douat-Casassus, C.; Quideau, S. *Org. Biomol. Chem.* **2010**, *8*, 5345



Esquema II.66

Por otro lado, Konaklieva y col. desarrollaron un método para la preparación de sistemas 1,2 y 1,3-dicarbonílicos a partir de 4,4-bis(metiltio)azetidin-2-onas diferentemente sustituidas en la posición C3. Los productos se obtuvieron mediante la ruptura selectiva del enlace N1-C4 del anillo β-lactámico (Esquema II.67).[109]



Esquema II.67

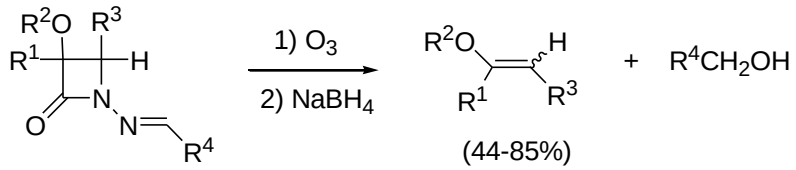
II.3.5. Ruptura de dos enlaces en el anillo de 2-azetidinona:

Se conocen muy pocos ejemplos en la literatura que describan la ruptura secuencial o simultánea de dos enlaces en el anillo de 2-azetidinona. La fragmentación de β-lactamas monocílicas por impacto electrónico en espectrometría de masas puede seguir dos patrones de ruptura diferentes: generar cetenas e iones iminio (camino A en el Esquema II.40), u olefinas e isocianatos (según el camino B). Mientras que la fotólisis fragmenta el anillo a través del

[109] Konaklieva, M. I.; Suwandi, L. S.; Kostova, M.; Deschamps, J. *Tetrahedron Lett.* **2011**, *52,* 1909.

camino A,[110] la pirólisis rompe el anillo de 2-azetidinona mediante una fragmentación de tipo B, con total retención de la estereoquímica.[111]

Durante la década de los 90, nuestro grupo de investigación fue el primero en describir la ruptura de tipo B en un anillo de 2-azetidinona en condiciones suaves. La nueva fragmentación descrita en *N*-ariliden o *N*-alquiliden-amino-β-lactamas, dio lugar a los correspondientes viniléteres mediante un tratamiento con ozono a -78ºC, seguido de una reducción con borohidruro sódico. (Esquema II.68).[112] Este proceso permitió la síntesis de una gran variedad de enoléteres sustituidos con buenos rendimientos y elevada estereoselectividad.



R^1 = H, Me R^2 = Me, Ph, Bn, Ac, *t*Bu

R^3 = Ph, 4-OMeC$_6$H$_4$, *i*Pr, *t*Bu R^4 = Ph, 4-OMeC$_6$H$_4$, *i*Pr, *t*Bu

Esquema II.68

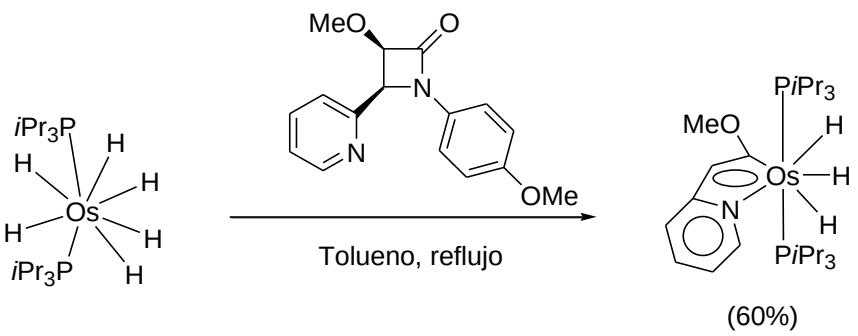
Recientemente, Sierra y col. describieron un nuevo mecanismo de ruptura concertada de los enlaces N1–C4 y C2–C3 del anillo β-lactámico a partir de 4-(2-piridil)-2-azetidinonas catalizado por osmio (Esquema II.69).[113] La adición de $OsH_6[(P(iPr_3)]_2$ al enlace C4–H de la β-lactama permite la participación activa del par de electrones solitario del osmio dando lugar al proceso de fragmentación tipo B del anillo.

110 Fischer, M. *Chem. Ver*. **1968**, *101*, 2669.

111 a) Paquette, L. A.; Wyvratt, M. J.; Allen, G. R. Jr. *J. Am. Chem. Soc*. **1970**, *92*, 1763. Para un ejemplo relacionado descrito en 2-azetidinonas, véase: b) Kappe, C. O.; Kollenz, G.; Netsch, K.-P.; Leung-Toung, R.; Wentrup, C. *J. Chem. Soc., Chem. Commun*. **1992**, 488.

112 a) Alcaide, B.; Pérez-Castells, J.; Polanco, C.; Sierra, M. A. *J. Org. Chem*. **1995**, *60*, 6012. b) Alcaide, B.; Miranda, M.; Pérez-Castells, J.; Sierra, M. A. *J. Org. Chem*. **1993**, *58*, 297.

113 Casarrubios, L.; Esteruelas, M. A.; Larramona, C.; Lledós, A.; Muntaner, J. G.; Oñate, E.; Ortuño, M. A.; Sierra, M A. *Chem. Eur. J.* **2015**, *21*, 16781.



Esquema II.69

II.4. Reacciones de fluoración en el núcleo indólico

Las moléculas orgánicas fluoradas han demostrado tener una gran utilidad en campos tales como la industria farmacéutica, agroquímica e incluso en ciencia de los materiales.[114] Esto es debido, en gran parte, a las propiedades únicas que ofrece la incorporación de flúor a un sustrato orgánico. El pequeño tamaño y la alta electronegatividad que presenta el flúor, junto con la fortaleza de sus enlaces con el carbono, implican que la sustitución de un átomo de hidrógeno o grupo hidroxilo de la molécula por éste provoque un efecto importante sobre las propiedades físico-químicas de la misma.

La influencia de la sustitución con flúor en las moléculas orgánicas en propiedades tales como logD, pKa, interacciones proteína-ligando y estabilidad metabólica se ha estudiado exhaustivamente,[115] lo que ha propiciado la aparición de nuevas metodologías que permiten la introducción de flúor de forma regio- y estereoselectiva en compuestos orgánicos utilizando reactivos sencillos y seguros de flúor.

Por otro lado, la desaromatización de indoles ha ganado especial importancia en síntesis orgánica a causa de la alta bioactividad que presentan las indolinas resultantes.[116] Por ello, en los últimos años se han descrito un gran

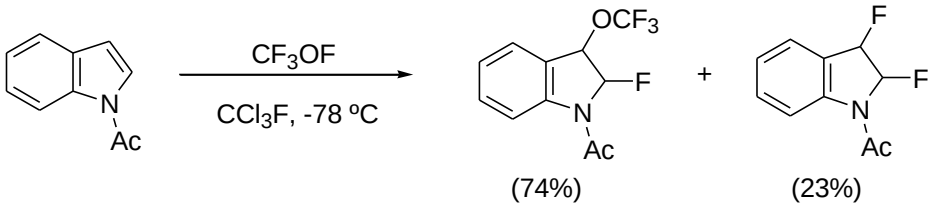
114 Kirsch, P. *Modern Fluoroorganic Chemistry;* Wiley-VCH: Weinheim, 2004.

115 a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. b) O'Hagan, D; *Chem. Soc. Rev.* **2008**, *37*, 308. c) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. d) Smart, B. E. *J. Fluorine Chem*. **2001**, *109*, 3.

116 Para revisiones de desaromatización de indoles y compuestos aromáticos véanse: a) Referencias 8a y 8b. b) Roche, S. P.; Tendoung, J,–J. Y.; Tréguier, B. *Tetrahedron* **2015**, *71*, 3549. Para indolinas bioactivas véanse: c) Referencia 8c. d) Cai, S.; Du, L.; Gerea, A. L.; King, J. B.; You, J.; Cichewicz, R. H. *Org. Lett.* **2013**, *15*, 4186. e) Zhang, D.; Song, H.;

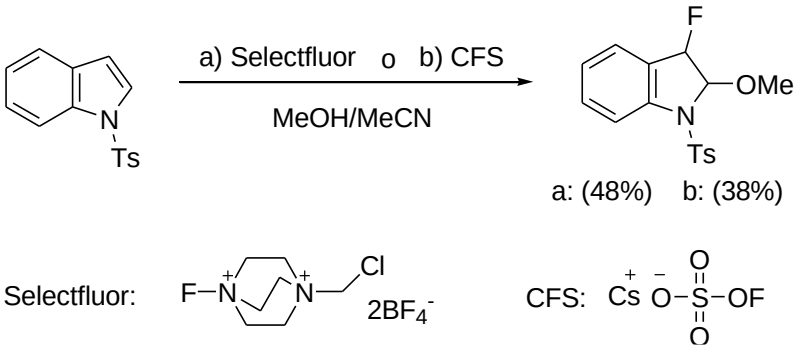
número de métodos de fluoración de indoles, que permiten obtener de manera directa una gran variedad de indolinas fluoradas. A continuación, se citarán algunos de los más importantes.

En 1977, Hesse y col. fueron los primeros en describir la síntesis de 2,3-difluoroindolinas y 2-fluoro-3-trifluorometoxindolinas a partir de indoles empleando el gas tóxico CF_3OF en freon a -78 ºC (Esquema II.70).[117]



Esquema II.70

Hasta 1994 no se describió ningún ejemplo adicional de fluoración de indoles. En este año, Widdowson y col. utilizaron tanto el Selectfluor como el fluoroxisulfato de cesio para describir la síntesis de 2-metoxi-3-fluoroindolinas con rendimientos moderados, por reacción de fluoración electrófila de *N*-tosilindoles (Esquema II.71).[118]



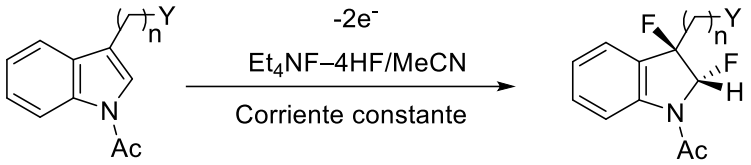
Esquema II.71

Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447. f) Ames, B. D.; Liu, X.; Walsh, C. T. *Biochemistry* **2010**, *49*, 8564. g) Zhao, H.; He, X.; Thurkauf, A.; Hoffman, D.; Kieltyka, A.; Brodbeck, R.; Primus, R.; Wasley, J. W. F. Bioorg. Med. Chem. Lett. **2002**, *12*, 3111. h) Goldbrunner, M.; Loidl, G.; Polossek, T.; Mannschreck, A.; Angerer, E. V. *J. Med. Chem.* **1997**, *40*, 3524. i) Bös, M.; Jenck, F.; Martin, J. R.; Moreau, J. L.; Mutel, V.; Sleight, A. J.; Widmer, U. *Eur. J. Med. Chem.* **1997**, *32*, 253. j) Hata, T.; Sano, Y.; Sugawara, R.; Matsumae, A.; Kanamori, K.; Shima, T.; Hoshi, T. *J. Antibiot. Ser. A* **1956**, *9*, 141.

117 Barton, D. H. R.; Hesse, R. H.; Jackman, G. P.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2604.

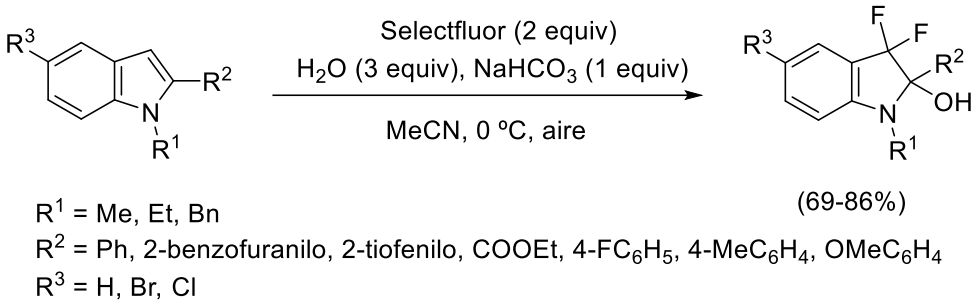
118 Hodson, H. F.; Madge, D. J.; Slawin, A. N. Z.; Widdowson, D. A.; Williams, D. J. *Tetrahedron* **1994**, *50*, 1899.

Por su parte, el grupo de Fuchigami llevó a cabo la difluoración de *N*-acetilindoles sustituidos en la posición C3 utilizando técnicas electroquímicas y $Et_4NF–4HF$ como fuente de flúor (Esquema II.72).[119] El isómero *trans* se obtiene de forma exclusiva o mayoritaria en todos los casos.



Esquema II.72

Jiao y col. describieron la síntesis de 3,3-difluoroindolin-2-oles por difluorohidroxilación de indoles diferentemente sustituidos utilizando Selectfluor como agente electrófilo de fluoración. La reacción transcurre con total regioselectividad, obteniéndose los compuestos difluorados con buenos rendimientos (Esquema II.73).[120]



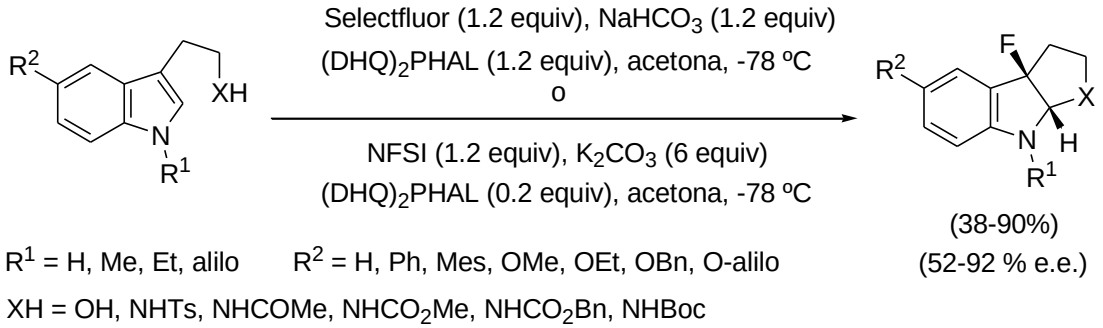
Esquema II.73

Gouverner y col. por su parte desarrollaron una ruta enantioselectiva para la obtención de indolinas fluoradas, describiendo así el primer ejemplo conocido de reacción de ciclofluoración asimétrica organocatalizada, usando como agentes de fluoración electrófilo Selectfluor o *N*-fluorobencenosulfonimida, y como agente quiral un alcaloide derivado de la Cinchona (Esquema II.74).[121]

119 a) Yin, B.; Wang, L.; Inagi, S.; Fuchigami, T. *Tetrahedron* **2010**, *66*, 6820. b) Hou, Y.; Higashiya, S.; Fuchigami, T. *J. Org. Chem*. **1997**, *62*, 8773.

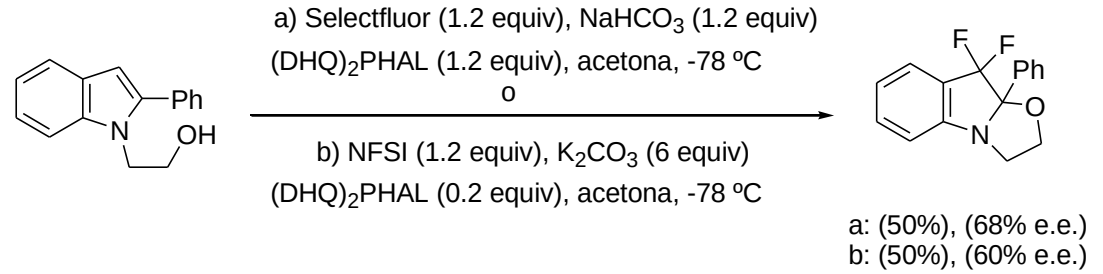
120 Lin, R.; Ding, S.; Shi, Z.; Jiao, N. *Org. Lett.* **2011**, *13*, 4498.

121 Véase referencia 10c.



Esquema II.74

Este mismo grupo de investigación describió el primer ejemplo de reacción de difluorooxiciclación asimétrica organocatalizada, mediante el ataque de un nucleófilo oxigenado unido al anillo de indol, utilizando las mismas condiciones de reacción (Esquema II.75).[122] El compuesto difluorado tricíclico se obtuvo con un rendimiento moderado y buenos excesos enantioméricos.

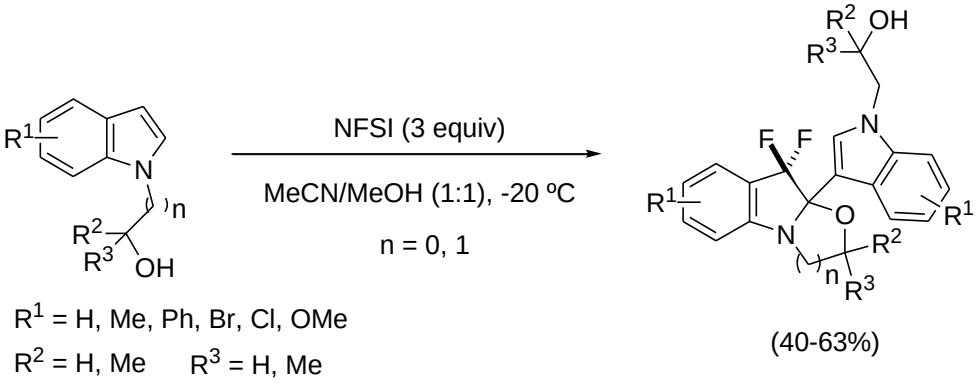


Esquema II.75

En los últimos años se han descrito reacciones de fluorofuncionalización de indoles a través de procesos tándem. Uno de estos ejemplos fue el descrito por Nguyen y col. para la síntesis de policiclos fluorados. Los autores describieron de esta forma una fluorofuncionalización en cascada a través de la formación de enlaces C–C, C–F y C–O vía fluoración electrófila (Esquema II.76).[123]

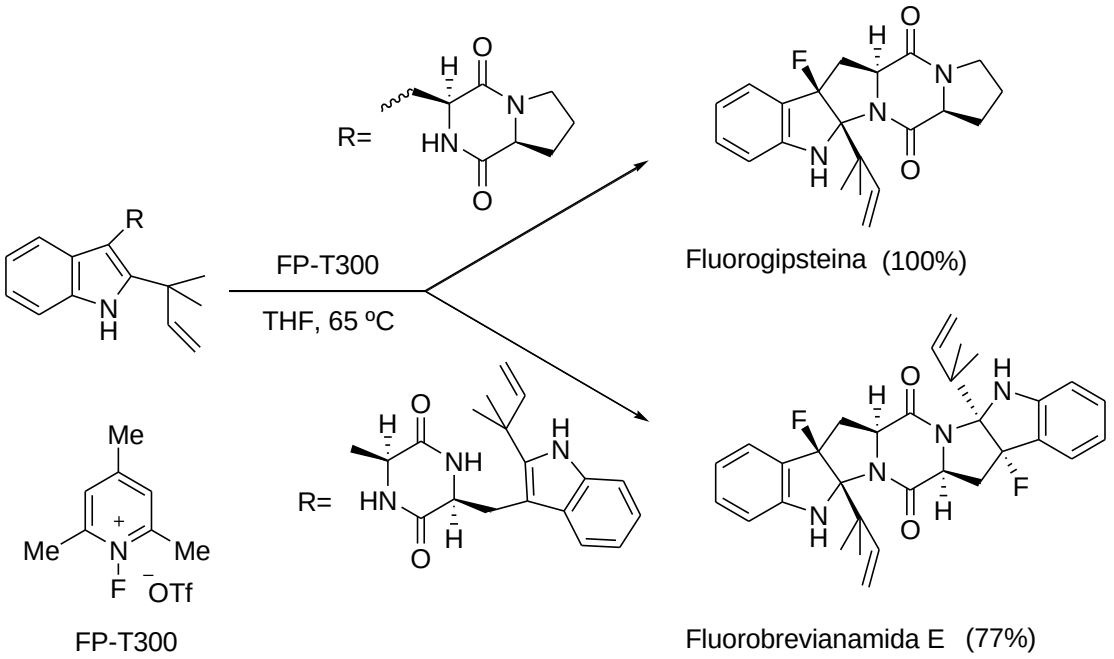
122 Véase referencia 10c.

123 a) Véase referencia 9a. b) Nguyen, T. M.; Duong, H. A.; Richard, J.–A.; Johannes, C. W.; Fu, P.; Kwong, D. J. W.; Lau, E. S. *Chem. Commun.* **2013**, *49*, 10602.



Esquema II.76

Asimismo, la reacción de fluoración de indoles se ha utilizado en diferentes rutas sintéticas que conducen a productos naturales.[124] Shibata y col. por su parte describieron la síntesis de la Fluorogipsteina y la Fluorobrevianamida E, mediante una secuencia de fluoración-ciclación utilizando la sal de fluropiridinio, FP-T300, como agente de fluoración (Esquema II.77).[125]

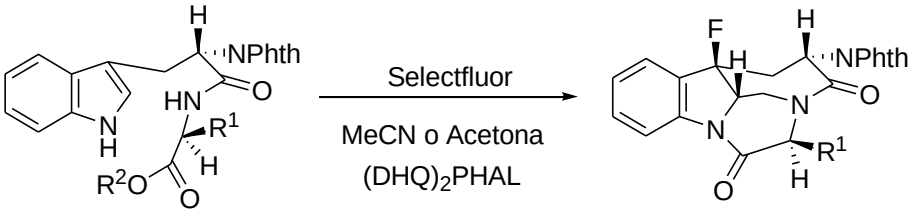


Esquema II.77

124 Para la síntesis de análogos fluorados de la protubina A, véase: a) Fujiwara, T.; Yasuda, H.; Nishimura, Y.; Nambu, H.; Yakura, T. *RSC Adv.* **2015**, *5*, 5464. Para la síntesis de BMS-204352 (Maxi Post), véase: b) Shibata, N.; Ishimaru, T.; Suzuki, E.; Kirk, K. L. *J.Org . Chem*. **2003**, *68*, 2494.

125 Shibata, N.; Tarui, T.; Doi, Y.; Kirk, K. L. *Angew. Chem. Int. Ed.* **2001**, *40*, 4461.

Por otro lado, Roche y col. han desarrollado recientemente una estrategia de desaromatización de indoles con incorporación de un átomo de flúor en su estructura, utilizando Selectfluor, que han aplicado a la obtención de análogos de los productos naturales Kapakahina B, Kapakahina F y Caetominina (Esquema II.78).[126]



R^1 = H, Me, Bn
R^2 = 4-ClC_6H_4, PFP

(25-42%)

Esquema II.78

126 Tréguier, B.; Roche, S. P. *Org. Lett.* **2014**, *16*, 278.

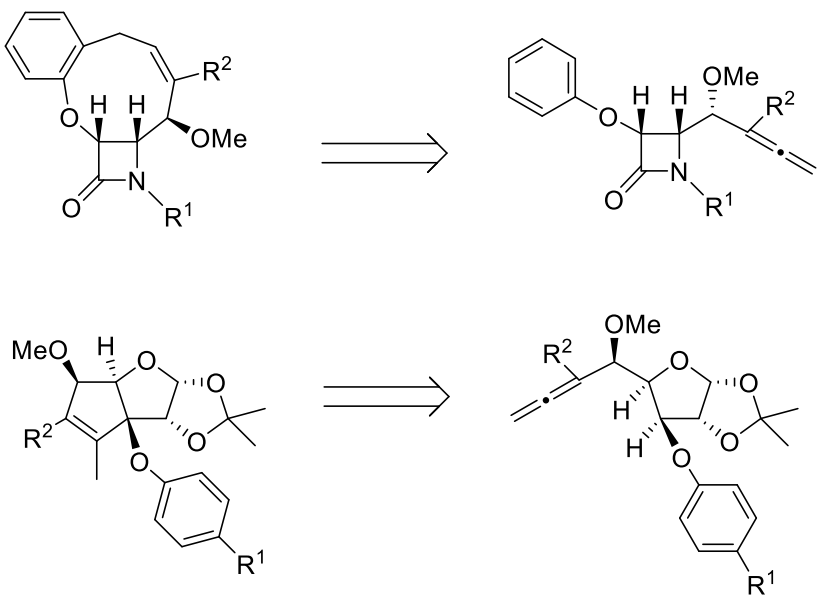
III. OBJETIVOS

III. OBJETIVOS

La presente tesis doctoral tiene como Objetivo General contribuir al desarrollo de nuevas metodologías de ciclación y transposición de alenos y cumulenos, catalizadas por metales, para la preparación de sistemas heterocíclicos estructuralmente novedosos.

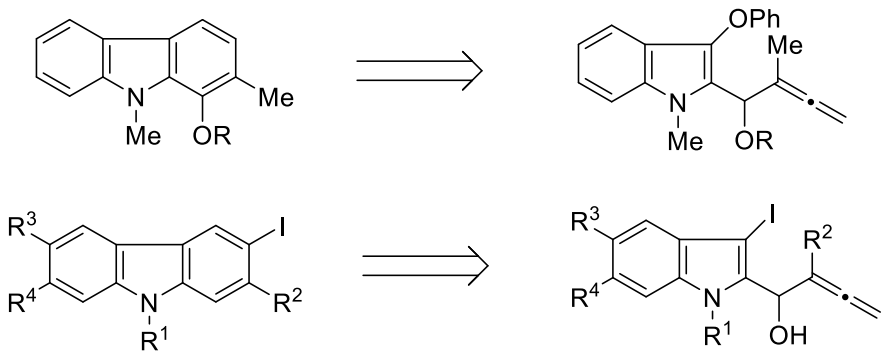
Para alcanzar este Objetivo General, la presente Memoria se ha divido en siete Capítulos, en los que se desarrollan las siete publicaciones a las que han dado lugar los resultados obtenidos, seguidos de una Discusión General de los mismos.

En el Capítulo 1 se estudiará la reactividad catalizada por oro (9-*endo* carbociclación frente a 5-*exo* hidroalquilación) de alenos unidos a núcleos de importancia biológica como son las β-lactamas o los azúcares (Esquema III.1).



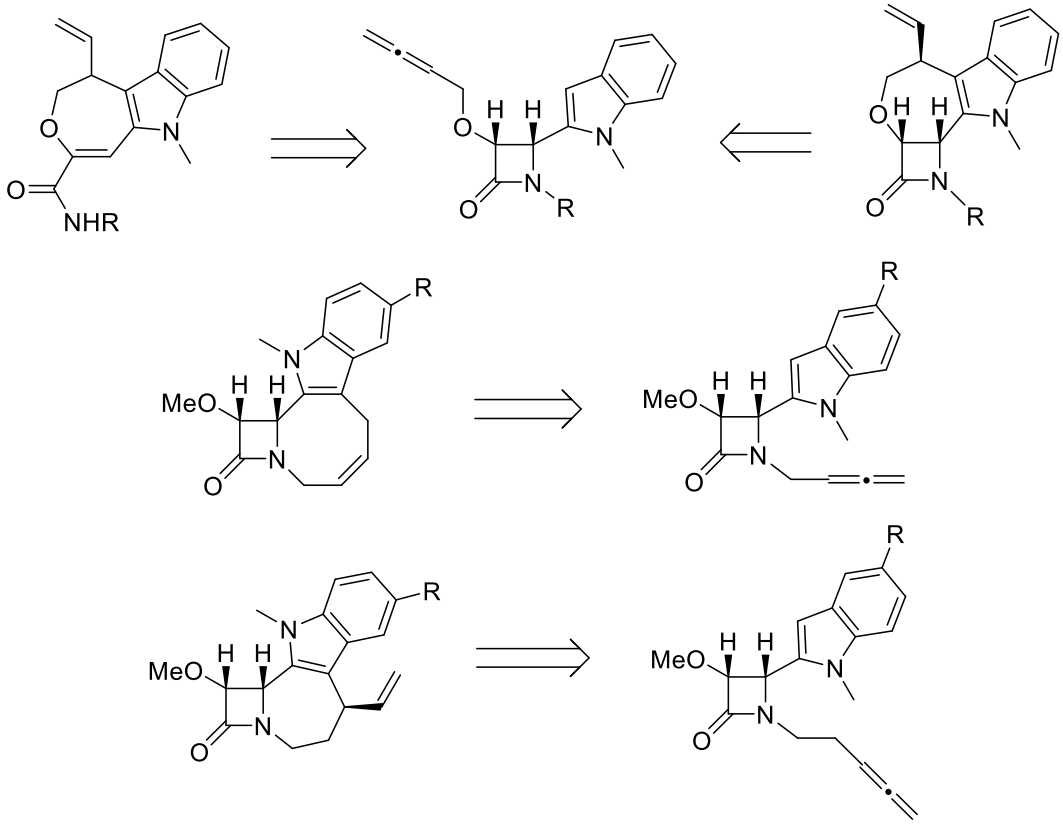
Esquema III.1

En el Capítulo 2 se abordará el estudio de los distintos patrones de reactividad de alenil-indoles diferentemente sustituidos en la posición C3 del anillo de indol (átomo de halógeno o grupo fenoxi) frente a catálisis de oro y/o paladio (Esquema III.2).



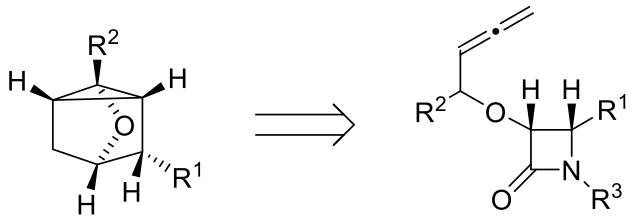
Esquema III.2

En el Capítulo 3 se estudiará la reacción de hidroarilación seguida de ruptura del enlace N1–C4 β-lactámico, catalizada por oro, en alenil-indoles unidos al núcleo de 2-azetidinona (Esquema III.3).



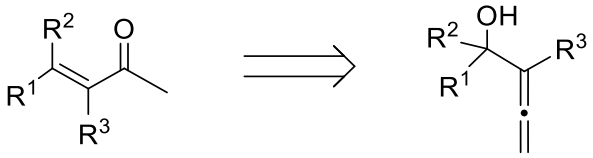
Esquema III.3

En el Capítulo 4 se llevará a cabo la síntesis de compuestos tensionados “tipo caja” a partir de alenil-β-lactamas utilizando catálisis de oro (Esquema III.4).



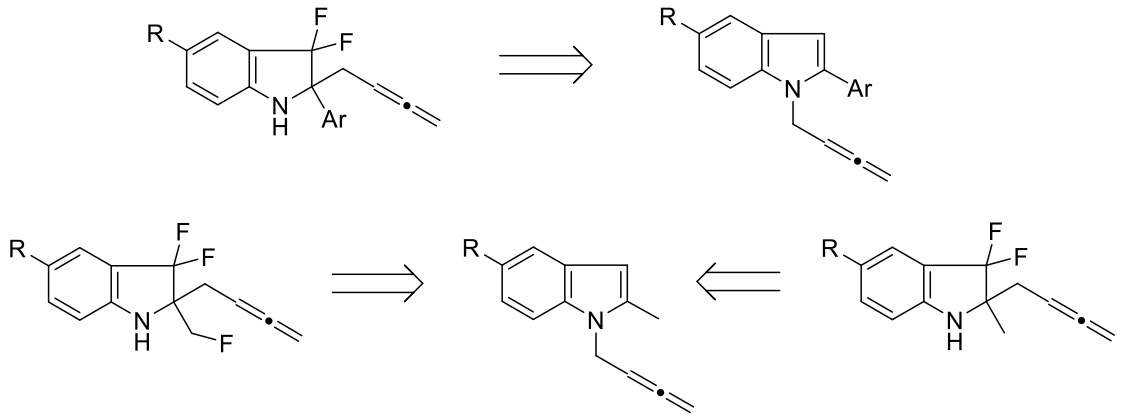
Esquema III.4

En el Capítulo 5 se describirá una nueva metodología de formación de cetonas α,β-insaturadas partiendo de α-alenoles en un medio catalítico sostenible, como son los protones o las sales de hierro (Esquema III.5).



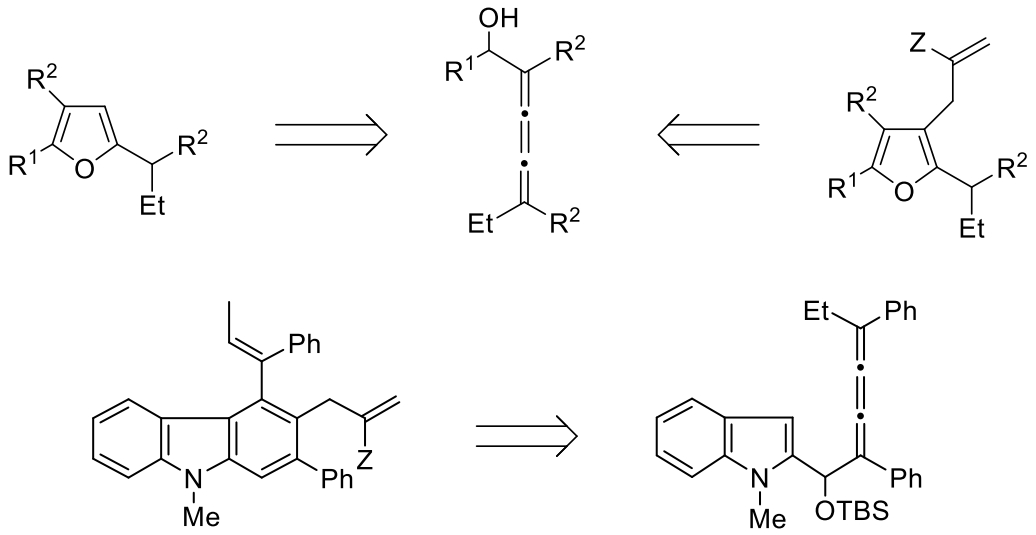
Esquema III.5

En el Capítulo 7 se abordará el estudio de la reactividad de *N*-alenil-indoles frente a Selectfluor y catálisis de hierro (Esquema III.6).



Esquema III.6

Por último, en el Capítulo 7 se estudiarán las diferentes reacciones de oxiciclación y carbociclación de distintos 2,3,4-trien-1-oles frente a catálisis de oro y paladio (Esquema III.7).



Esquema III.7

IV. CAPÍTULO 1

IV.1. Gold-catalysed tuning of reactivity in allenes: 9-*endo* hydroarylation versus formal 5-*exo* hydroalkylation

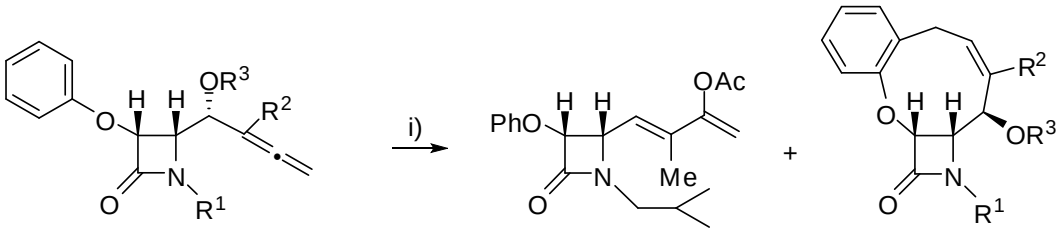
The divergent gold-catalysed reactivity (C_{sp2}–H versus *C_{sp3}–H) of aryloxy-tethered allenes has been uncovered.*

Chem. Commun. **2013**, *49*, 1282

IV.2. Communication

The preparation of medium-sized ring polycycles through selective C–H bond activation is a big challenge. In this regard, the goldcatalysed intramolecular hydroarylation of allenes[1] may be a possible solution to produce eight- or nine-membered carbocycles, although this achievement has not yet been accomplished. We present here an unprecedented Au-catalyzed 9-*endo* carbocyclization of aryl allenes as a powerful synthetic tool to obtain novel nine-membered annulated β-lactam derivatives.[2] In addition, it is shown that the outcome of the reaction (9-*endo* hydroarylation versus formal 5-*exo* hydroalkylation) can be modulated by the allene tether.

To explore the reactivity of (aryl)allene-tethered 2-azetidinones **1** towards hydroarylation, we selected acetate **1a** as a model substrate. As a first try, we were happy to notice that although the reaction of derivative **1a** afforded dienol ester **2a** as a major component (34% isolated yield), the intramolecular hydroarylation adduct **3a** was also isolated as a minor component (13%) (Scheme IV.1).



(**+**)-**1a** R^1 = isobutyl, R^2 = Me, R^3 = Ac
(**+**)-**1b** R^1 = isobutyl, R^2 = Me, R^3 = Me
(**+**)-**1c** R^1 = isobutyl, R^2 = Ph, R^3 = Me
(**+**)-**1d** R^1 = Bn, R^2 = Me, R^3 = Me
(**+**)-**1e** R^1 = Bn, R^2 = Ph, R^3 = Me
(**+**)-**1f** R^1 = isopropyl, R^2 = Me, R^3 = Me
(**+**)-**1g** R^1 = isopropyl, R^2 = Ph, R^3 = Me
(**+**)-**1h** R^1 = 2-methylallyl, R^2 = Ph, R^3 = Me

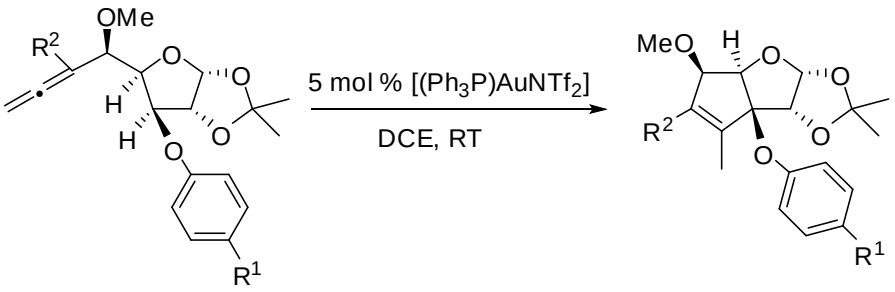
(**–**)-**2a** (34%)

(**+**)-**3a** (13%)
(**+**)-**3b** (72%)
(**+**)-**3c** (60%)
(**+**)-**3d** (58%)
(**+**)-**3e** (69%)
(**+**)-**3f** (65%)
(**+**)-**3g** (59%)
(**+**)-**3h** (63%)

Scheme IV.1. Controlled intramolecular gold-catalysed hydroarylation of allenyl-tethered arenes **1a–h**. i) 5 mol % [$(Ph_3P)AuNTf_2$], DCE, μwave, 110 °C (RT for **1a**). Ac = COMe. Tf = Triflyl. DCE = 1,2-Dichloroethane.

Thus, in order to prevent the [3,3]-sigmatropic rearrangement involving the acetate group,[3] the hydroxy functionality was protected in the form of methyl ether. Fortunately, treatment of allene **1b** with [(Ph_3P)AuNTf_2] in 1,2-dichloroethane at room temperature gave full conversion; benzo[*b*]oxonine **3b** being isolated in 51% yield in a totally selective fashion (Scheme IV.1).[4] Clearly, applying microwave irradiation and using deactivated silica gel during purification resulted in an increased 72% yield for adduct **3b**. Similar figures were observed for tricyclic products **3c–h** without harming the sensitive β-lactam ring (Scheme IV.1). Remarkably, this rare 9-*endo* carbocyclization reaction was the only operative cyclization mode.

We also decided to undertake a study of the potential use of more diverse substrates in this novel allene hydroarylation mode. Thus, (aryloxy)allenyl-tethered sugars **4a–e** were studied by using the optimum reaction conditions obtained for (aryloxy)allenyl-tethered 2-azetidinones **1b–h**. Remarkably, we found a divergent reactivity compared with the transformation found with allenes **1**; instead of the expected hydroarylation adducts, tricycles **5** arising from a rare 5-*exo* hydroalkylation were obtained (Scheme IV.2). Notably, the direct and selective functionalization of an otherwise inactive C_{sp3}–H bond has been achieved.[5]

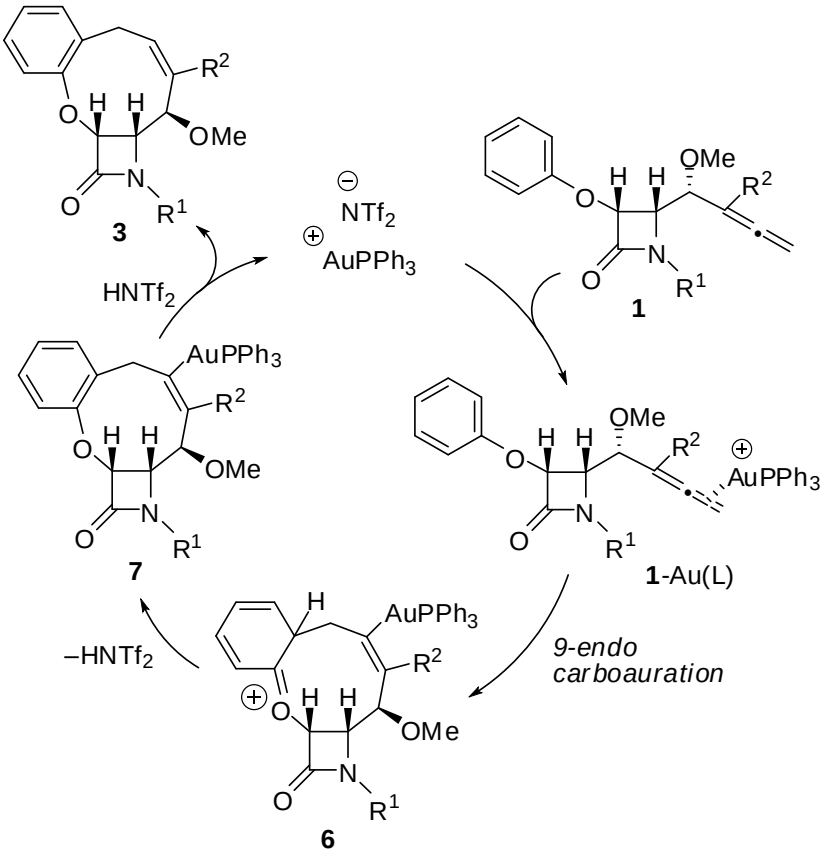


(**–**)-**4a** R^1 = H, R^2 = Me
(**–**)-**4b** R^1 = H, R^2 = Et
(**–**)-**4c** R^1 = H, R^2 = $BnOCH_2$
(**–**)-**4d** R^1 = Br, R^2 = Me
(**–**)-**4e** R^1 = Br, R^2 = $BnOCH_2$

(**+**)-**5a** (46%)
(**+**)-**5b** (34%)
(**+**)-**5c** (48%)
(**+**)-**5d** (35%)
(**+**)-**5e** (41%)

Scheme IV.2 Controlled intramolecular formal 5-*exo* hydroalkylation reaction of allenyl-tethered arenes **4a–e** under gold-catalysed conditions.

Besides, regioselectivity can be completely reversed by using the sugar derivative, thus favouring the cyclization of the aryloxy ether group toward the central allene carbon over the cyclization towards the terminal allene carbon. The reaction of allenes **4** did take place with complete stereoselectivity, representing a selective method to afford fused cyclopentenes **5** bearing a quaternary stereocenter.[6] Complete conversion was observed by TLC and ^{1}H NMR analysis of the crude reaction mixtures of allenols **4**, and no side-products from isomerisation or polymerization reactions were detected. Unfortunately, some decomposition was observed on sensitive tricycles **5** during purification by flash chromatography, which may be responsible for the moderate isolated yields.



Scheme IV.3 Mechanistic explanation for the gold-catalysed hydroarylation of allenyl-tethered oxyarenes **1**.

A possible pathway for the gold-catalysed achievement of tricycles **3** from allenyl-tethered arenes **1** may initially involve the formation of a complex **1**–Au(L) through coordination of the gold salt to the distal allenic double bond. Next, chemo-

and regioselective 9-*endo* carboauration forms species **6**. Attack from the activated 2-position of the arene occurs as a result of the stability of the intermediate oxonium cation type **6**. Loss of proton generates neutral species **7**, which followed by protonolysis of the carbon–gold bond afforded fused ninemembered cycles **3** with concurrent regeneration of the gold catalyst (Scheme IV.3).

Density functional theory (DFT) calculations have been carried out to gain more insight into the reaction mechanism of the above discussed gold-catalysed 9-*endo* hydroarylation reaction. The corresponding computed reaction profile of the model allenyl-β-lactam reactant **1M** with [(Me_3P)$AuNTf_2$] as catalyst is illustrated in Figure IV.1, which shows the corresponding free energies in CH_2Cl_2 solution (PCM-M06/def2-SVP//PCM-B3LYP/def2-SVP level). Our calculations suggest that the reaction starts with the exergonic coordination of the $AuPMe_3^+$ catalyst to the distal double bond of the allenic moiety of **1M** (ΔG_{298} = –9.4 kcal mol^{-1}). Then, the 9-*endo* carbocyclization reaction to produce the nine-membered ring tricyclic intermediate **2M** occurs through the transition state **TS1**. This saddle point is associated with the nucleophilic addition of the activated *ortho*-carbon atom to the electrophilic gold complex. Although the activation barrier of this model reaction is relatively high ($\Delta G_{a,298}$ = 29.9 kcal mol^{-1}),[7] this process is kinetically and thermodynamically favoured over the corresponding carbocyclization reactions leading to 7- or 8-membered ring intermediates.[8] This result is in agreement with the exclusive formation of nine-membered ring tricyclic compounds **3**, as experimentally observed. Intermediate **2M** is then transformed into the neutral complex **4M** *via* the initially formed complex **3M** (where the NTf_2^- anion is weakly bonded to **2M**) through transition state **TS2**. The latter saddle point is associated with the easy and exergonic proton abstraction in **2M** by the NTf_2^- anion ($\Delta G_{a,298}$ = 1.4 kcal mol^{-1} and (ΔG_{298} = -16.9 kcal mol^{-1}, from **3M**). The addition of the readily formed $NHTf_2$ to **4M** forms complex **5M**, which evolves into complex **6M** via **TS3** (associated with the protonolysis reaction of the carbon–gold bond). The latter process is also highly exergonic (ΔG_{298} = -19.4 kcal mol^{-1}) and proceeds with a very low activation barrier ($\Delta G_{a,298}$ = 0.9 kcal mol^{-1}).[9,10] Thus, it can be concluded that the initial 9-*endo* carbocyclization reaction constitutes the bottle-neck of the process in view of the corresponding endergonicity and relatively high activation barrier. Finally, the

reaction ends up with the release of the $AuPMe_3^+$ catalyst, which is coordinated to the endocyclic C=C double bond of **6M**, to produce the final tricyclic species **7M**.

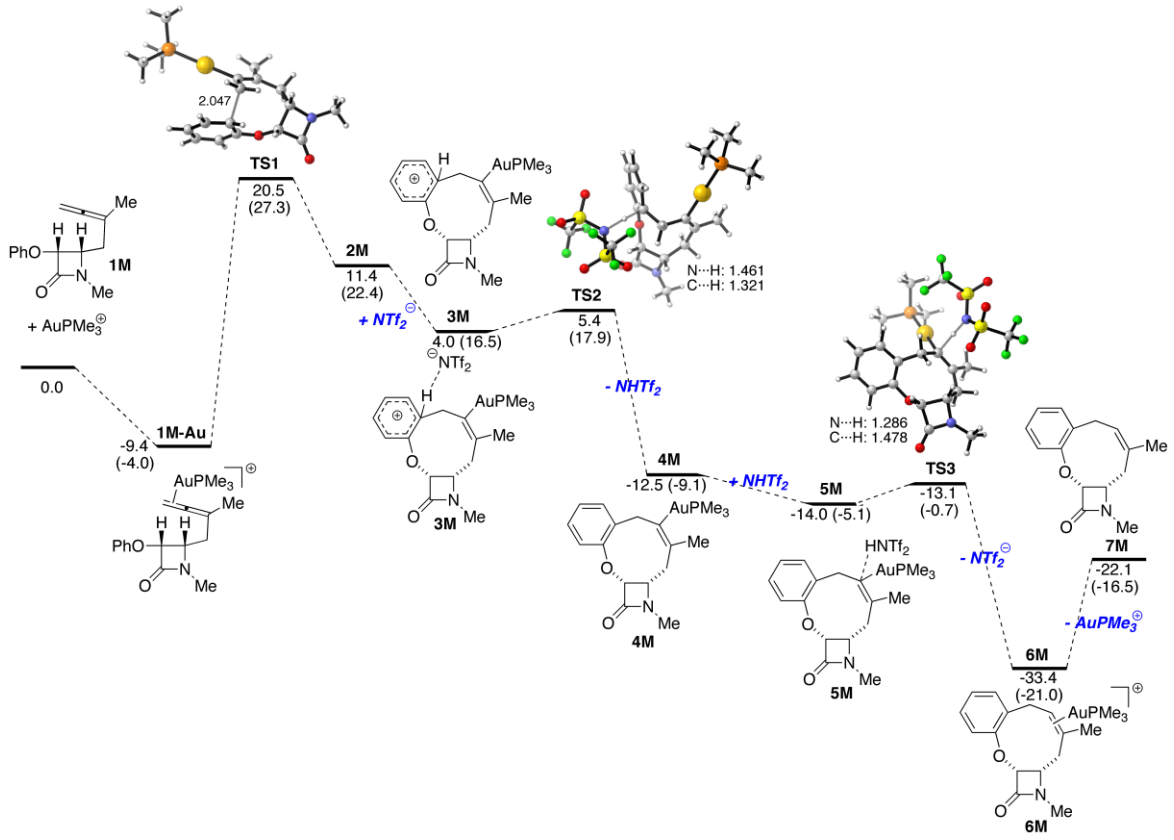
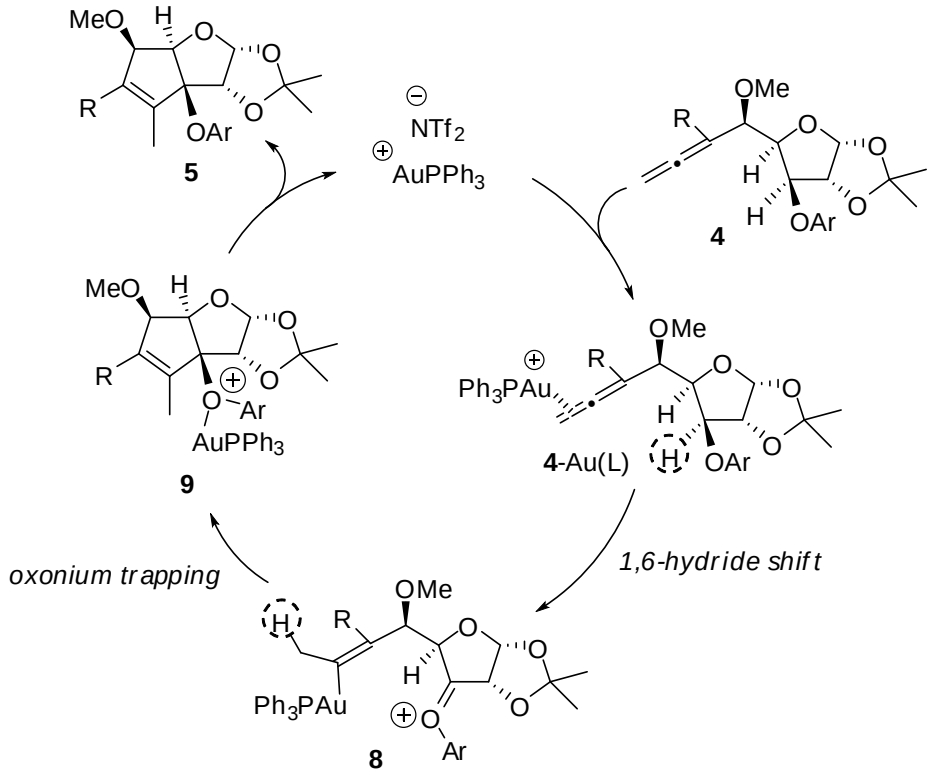


Figure IV.1 Computed reaction profile for the reaction of allenyl-β-lactam **1M** and [(PMe_3)$AuNTf_2$] catalyst.[11]

A mechanistic rationale for the gold-catalysed conversion of allenyl-tethered sugars **4** into fused cyclopentenes **5** is more intricate. It is worth noting that the cyclization affords adducts **5** from an allene umpolung hydrofunctionalization instead of that from the usually preferred conventional hydrofunctionalization. The pathway proposed in Scheme IV.4 looks valid for the formation of tricycles of type **5**. It could be presumed that the initially formed gold complex **4**–Au(L), through coordination of the gold salt to the distal allenic double bond, undergoes a 1,6-hydride shift (rare transfer of hydride *versus* normal nucleophilic group attack), giving rise to the oxonium species **8**. Intramolecular trapping of the oxonium group by the alkenylgold moiety in intermediates **8** generates cationic species **9**, through

formal 5-*exo* hydroalkylation. Finally, demetalation yields fused cyclopentenes **5** and regenerates the gold catalyst (Scheme IV.4).



Scheme IV.4 Mechanistic explanation for the gold-catalyzed formal 5-*exo* hydroalkylation of allenyl-tethered oxyarenes **4**.

Preliminary DFT calculations on the model (aryloxy)allenyltethered sugar species **8M** (see Figure IV.S3 in the IV.3. Experimental Section) indicate that the direct 1,6-hydride shift from the distal double bond-coordinated complex **8M–Au** occurs with a relatively high activation barrier ($\Delta G_{a,298}$ = 37.7 kcal mol^{-1}, that is 25.2 kcal mol^{-1} above the separate reactants **8M** and $AuPMe_3^+$). This step is followed by the highly exergonic C–C bond forming reaction (*i.e.* oxonium trapping) *via* TS5 with an activation barrier of 26.1 kcal mol^{-1}. Further DFT calculations involving the NTf_2-mediated 1,6-hydride shift andmore realistic species leading to a processmore compatible with a reaction at room temperature are currently underway.

In conclusion, the divergent gold-catalysed reactivity (C_{sp2}–H *versus* C_{sp3}–H) of aryloxy-tethered allenes has been studied. We report herein an efficient gold-

catalysed 9-*endo* carbocyclization to fused tricyclic β-lactams from easily accessible aryl allene substrates under mild conditions. In salient contrast to the reaction of (aryloxy)allenyl-tethered 2-azetidinones, the allenyl sugar derivatives provided the 5-*exo* hydroalkylation adducts as the sole products. The reactions were found to proceed with complete control of product regio- and chemoselectivity.

IV.3. Experimental Section

General Methods: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, Bruker AMX-500, Bruker Avance-300, Varian VRX-300S or Bruker AC-200. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{13}C, 76.9 ppm). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. Specific rotation $[\alpha]_D$ is given in 10^{-1} deg cm^2 g^{-1} at 20 °C, and the concentration (*c*) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

Starting (aryloxy)allenol-tethered 2-azetidinones were prepared from 4-oxoazetidine-2-carbaldehydes via regiocontrolled indium-mediated Barbier-type carbonyl–allenylation reaction in aqueous media using our methodology: B. Alcaide, P. Almendros, C. Aragoncillo, M. C. Redondo and M. R. Torres, *Chem. Eur. J.,* 2006, **12**, 1539.

Preparation of Allenyl Acetate (+)-1a. Triethylamine (0.94 mmol) and acetic anhydride (0.47 mmol) were sequentially added dropwise via syringe to a solution of the corresponding α-allenic alcohol (119 mg, 0.39 mmol) and DMAP (cat) in dichloromethane (4 mL) at 0 °C under argon. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. The crude mixture was diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous ammonium chloride (3 x 5 mL) and brine (3 x 5 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes (1:2) gave 78 mg (58%) of analytically pure α-allenic acetate (+)-**1a** as a colorless oil; $[\alpha]_D$ = +7.7 (*c* = 0.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, 3H, *J* = 6.7 Hz, Me), 1.00 (d, 3H, *J* = 6.7 Hz, Me), 1.82 (t, 3H, *J* = 3.2 Hz, Me), 2.03 (m, 1H, CH isobut), 2.13 (s, 3H, COMe), 2.96 (dd, 1H, *J* = 13.8, 6.1 Hz, NCH*H*), 3.33 (dd, 1H, *J* = 13.7, 8.6 Hz, NC*H*H), 4.26 (dd, 1H, *J* = 6.7, 5.0 Hz, H4), 4.78 (m, 2H, $=CH_2$), 5.28 (d, 1H, *J* = 5.0 Hz, H3), 5.60 (dt, 1H, *J* = 6.7, 2.0 Hz, OCH), 7.04 (t, 1H, *J* = 7.3 Hz, Ar), 7.09 (d, 2H, *J* = 7.7 Hz, Ar), 7.32 (m, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.9 (C=*C*=CH_2), 169.7 (COMe), 166.6 (CO), 157.7, 129.5 (Ar, 2CH), 122.3 (Ar, CH), 115.8 (Ar, 2CH), 97.6, 80.0 (CH, H3), 77.6 (C=*C*H_2), 72.4 (OCH), 58.5 (CH, H4), 49.4 (CH_2 isobut), 27.0 (CH isobut), 21.0 (Me), 20.4 (Me), 20.2 (Me), 16.4 (Me); IR ($CHCl_3$): ν = 2995, 1944, 1757, 1725 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{25}NO_4$ $[M]^+$: 343.1784; found: 343.1797.

General Procedure for the Synthesis of Methoxy Allenes 1b–h and 4a–e. Tetrabutyl ammonium iodide (cat), 50% aqueous sodium hydroxide (18 mL) and dimethyl sulfate (0.60 mmol) were sequentially added at room temperature to a solution of the corresponding α-allenol (0.92 mmol) in dichloromethane (18 mL). The reaction was stirred until disappearance of the starting material (TLC). Then aqueous ammonia (30%) was added (2.5 mL), before being partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (3 x 15 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/hexanes mixtures gave analytically pure compounds. Spectroscopic and analytical data for some representative pure forms of **1** and **4** follow.

Methoxy Allene (+)-1b. From 355 mg (1.18 mmol) of the corresponding α-allenic alcohol, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave the methoxy allene (+)-**1b** (167 mg, 45%) as a colorless oil; $[\alpha]_D$ = +11.2 (*c* = 0.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, 3H, *J* = 6.7 Hz, Me), 0.96 (d, 3H, *J* =

6.7 Hz, Me), 1.70 (t, 3H, *J* = 3.2 Hz, Me), 2.06 (m, 1H, CH isobut), 3.14 (dd, 1H, *J* = 13.6, 6.3 Hz, NCH*H*), 3.26 (dd, 1H, *J* = 13.4, 8.2 Hz, NC*H*H), 3.33 (s, 3H, OMe), 4.00 (m, 1H, OCH), 4.02 (d, 1H, *J* = 5.9 Hz, H4), 4.41 (m, 1H, =CH*H*), 4.62 (m, 1H, =C*H*H), 5.22 (d, 1H, *J* = 4.1 Hz, H3), 7.00 (t, 1H, *J* = 7.3 Hz, Ar), 7.02 (d, 2H, *J* = 6.7 Hz, Ar), (m, 3H, Ar), 7.28 (m, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.3 (C=*C*=CH_2), 166.6 (CO), 158.0, 129.4 (Ar, 2CH), 121.9 (Ar, CH), 115.6 (Ar, 2CH), 94.7, 82.6 (CH, H3), 79.7 (OCH), 74.9 (C=*C*H_2), 59.2 (CH, H4), 55.7 (OMe), 49.7 (NCH_2), 27.0 (CH isobut), 20.4 (Me), 20.2 (Me), 14.4 (Me); IR ($CHCl_3$): ν = 2992, 1947, 1756 cm^{-1}; HRMS (ES): calcd for $C_{19}H_{25}NO_3$ [*M*]$^+$: 315.1834; found: 315.1832.

Methoxy Allene (+)-1c. From 322 mg (0.89 mmol) of the corresponding α-allenic alcohol, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave the methoxy allene (+)-**1c** (216 mg, 65%) as a colorless oil; $[\alpha]_D$ = +16.7 (*c* = 0.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, 3H, *J* = 6.7 Hz, Me), 0.98 (d, 3H, *J* = 6.7 Hz, Me), 2.08 (m, 1H, CH isobut), 3.20 (dd, 1H, *J* = 13.6, 6.3 Hz, NCH*H*), 3.32 (dd, 1H, *J* = 13.4, 8.3 Hz, NC*H*H), 3.41 (s, 3H, OMe), 4.19 (dd, 1H, *J* = 9.1, 4.8 Hz, H4), 4.59 (d, 1H, *J* = 9.1 Hz, OCH), 4.83 (d, 1H, *J* = 12.4 Hz, =CH*H*), 5.00 (d, 1H, *J* = 12.5 Hz, =C*H*H), 5.14 (d, 1H, *J* = 4.8 Hz, H3), 6.80 (d, 2H, *J* = 7.7 Hz, Ar), 6.96 (t, 1H, *J* = 7.3 Hz, Ar), 7.23 (m, 3H, Ar), 7.35 (t, 2H, *J* = 7.0 Hz, Ar), 7.46 (d, 2H, *J* = 7.0 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.5 (C=*C*=CH_2), 166.7 (CO), 157.9, 134.0, 129.2 (Ar, 2CH), 128.6 (Ar, CH), 127.2 (Ar, 3CH), 121.9 (Ar, CH), 115.7 (Ar, 3CH), 102.6, 81.5 (CH, H3), 79.6 (OCH), 78.1 (C=*C*H_2), 59.6 (CH, H4), 55.6 (OMe), 49.8 (NCH_2), 27.1 (CH isobut), 20.5 (Me), 20.2 (Me); IR ($CHCl_3$): ν = 2999, 1944, 1753 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{27}NO_3$ [*M*]$^+$: 377.1991; found: 377.1997.

Methoxy Allene (+)-1d. From 57 mg (0.17 mmol) of the corresponding α-allenic alcohol, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave the methoxy allene (+)-**1d** (31 mg, 52%) as a colorless oil; $[\alpha]_D$ = +15.0 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.63 (t, 3H, *J* = 3.2 Hz, Me), 3.17 (s, 3H, OMe), 3.91 (dd, 1H, *J* = 9.2, 4.8 Hz, H4), 4.03 (d, 1H, *J* = 9.2 Hz, OCH), 4.32 (m, 1H, =CH*H*), 4.46 (d, 1H, *J* = 14.6 Hz, NCH*H*), 4.57 (m, 1H, =C*H*H), 4.69 (d, 1H, *J* = 14.6 Hz, NC*H*H), 5.19 (d, 1H, *J* = 4.8 Hz, H3), 7.00 (t, 1H, *J* = 7.7 Hz, Ar), 7.02 (d, 2H, *J* = 8.0 Hz, Ar), 7.30 (m, 3H, Ar), 7.36 (m, 4H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.3 (C=*C*=CH_2), 166.6 (CO), 136.4, 129.3 (Ar, 2CH), 128.6 (Ar, 3CH) , 128.5 (Ar, 2CH), 127.5, 122.0 (Ar, CH), 115.6 (Ar, 2CH), 94.5, 82.4 (CH, H3), 79.9 (OCH), 74.9 (C=*C*H_2), 58.6 (CH, H4), 55.6 (OMe), 45.9 (NCH_2), 14.9 (Me); IR ($CHCl_3$): ν = 2996, 1945, 1759 cm^{-1}; HRMS (ES): calcd for $C_{22}H_{23}NO_3$ [*M*]$^+$: 349.1678; found: 349.1689.

Methoxy Allene (+)-1e. From 215 mg (0.54 mmol) of the corresponding α-allenic alcohol, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave the methoxy allene (+)-**1e** (120 mg, 54%) as a colorless oil; $[\alpha]_D$ = +8.7 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.18 (s, 1H, OMe), 4.00 (dd, 1H, *J* = 9.4, 4.8 Hz, H4), 4.39 (d, 1H, *J* = 14.6 Hz, NCH*H*), 4.47 (d, 1H, *J* = 9.3 Hz OCH), 4.59 (d, 1H, *J* = 12.5 Hz, =CH*H*), 4.69 (d, 1H, *J* = 14.6 Hz, NC*H*H), 4.84 (d, 1H, *J* = 12.5 Hz, =C*H*H), 5.00 (d, 1H, *J* = 5.0 Hz, H3), 6.70 (d, 2H, *J* = 7.9 Hz, Ar), 6.88 (t, 1H, *J* = 7.3 Hz, Ar), 7.18 (m, 6H, Ar), 7.25 (m, 6H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.6 (C=*C*=CH_2), 166.2 (CO), 157.8, 136.2, 134.2, 129.2 (Ar, 2CH), 128.6 (Ar, 4CH), 128.5 (Ar, 2CH), 128.4 (Ar, CH), 127.5 (Ar, CH), 127.2 (Ar, 2CH), 121.9 (Ar, CH), 115.7 (Ar, 2CH), 102.1, 81.6 (CH, H3), 79.9 (OCH), 77.9 (C=*C*H_2), 58.6 (CH, H4), 55.5 (OMe), 46.1 (NCH_2); IR ($CHCl_3$): ν = 2993, 1946, 1756 cm^{-1}; HRMS (ES): calcd for $C_{27}H_{25}NO_3$ [*M*]$^+$: 411.1834; found: 411.1846.

Methoxy Allene (+)-1f. From 314 mg (1.09 mmol) of the corresponding α-allenic alcohol, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave the methoxy allene (+)-**1f** (210 mg, 64%) as a colorless oil; $[\alpha]_D$ = +15.2 (*c* = 0.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (d, 3H, *J* = 6.6 Hz, Me), 1.39 (d, 3H, *J* = 6.6 Hz, Me), 1.70 (t, 3H, *J* = 3.2 Hz, Me), 3.34 (s, 3H, OMe), 3.90 (sept, 1H, *J* = 6.1 Hz, NCH), 3.92 (m, 1H, OCH), 4.01 (t, 1H, *J* = 4.7 Hz, H4), 4.40 (m, 1H,=CH*H*), 4.61 (m, 1H, =C*H*H), 5.14 (d, 1H, *J* = 4.5 Hz, H3), 6.99 (t, 1H, *J* = 7.3 Hz, Ar), 7.03 (d, 2H, *J* = 7.7 Hz, Ar), 7.28 (m, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.5 (C=*C*=CH_2), 165.8 (CO), 158.0, 129.8 (Ar, 2CH), 121.9 (Ar, CH) , 115.7 (Ar, 2CH), 94.5, 82.5 (CH, H3), 79.1 (OCH), 74.8 (C=*C*H_2), 58.6 (CH, H4), 55.6 (OMe), 46.0 (NCH), 21.2 (Me), 19.9 (Me), 14.3 (Me); IR ($CHCl_3$): ν = 2998, 1948, 1753 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{23}NO_3$ [*M*]$^+$: 301.1678; found: 301.1684.

Methoxy Allene (+)-1g. From 259 mg (0.74 mmol) of the corresponding α-allenic alcohol, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave the methoxy allene (+)-**1g** (240 mg, 89%) as a colorless oil; $[\alpha]_D$ = +11.9 (*c* = 0.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, 3H, *J* = 6.7 Hz, Me), 1.40 (d, 3H, *J* = 6.8 Hz, Me), 3.43 (s, 3H, OMe), 3.95 (sept, 1H, *J* = 6.9 Hz, NCH), 4.21 (dd, 1H, *J* = 9.2, 5.0 Hz, H4), 4.51 (d, 1H, *J* = 9.2 Hz, OCH), 4.82 (d, 1H, *J* = 12.4 Hz, =CH*H*), 5.00 (d, 1H, *J* = 12.4 Hz, =C*H*H), 5.05 (d, 1H, *J* = 5.0 Hz, H3), 6.78 (d, 2H, *J* = 7.7 Hz, Ar), 6.96 (t, 1H, *J* = 7.3 Hz, Ar), 7.23 (m, 3H, Ar), 7.34 (t, 2H, *J* = 7.0 Hz, Ar), 7.47 (d, 2H, *J* = 7.1 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.7 (C=*C*=CH_2), 165.9 (CO), 157.9, 134.7, 129.2 (Ar, 2CH), 128.5 (Ar, 3CH), 127.2 (Ar, 2CH), 121.8 (Ar, CH), 115.7 (Ar, 2CH), 102.5, 81.5 (CH, H3), 79.1 (OCH), 78.0 (C=*C*H_2), 59.2 (CH, H4), 55.6 (OMe), 46.1 (NCH), 21.4 (Me), 20.0 (Me); IR ($CHCl_3$): ν = 2995, 1945, 1748 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{25}NO_3$ [*M*]$^+$: 363.1834; found: 363.1836.

Methoxy Allene (+)-1h. From 105 mg (0.29 mmol) of the corresponding α-allenic alcohol, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave the methoxy allene (+)-**1h** (52 mg, 49%) as a colorless oil; $[\alpha]_D$ = +9.0 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.76 (s, 3H, Me), 3.38 (s, 3H, OMe), 3.91 (d, 1H, *J* = 15.2 Hz, NCH*H*), 4.21 (dd, 1H, *J* = 9.2, 4.8 Hz, H4), 4.14 (d, 1H, *J* = 15.4 Hz, NC*H*H), 4.61 (d, 1H, *J* = 9.2 Hz, OCH), 4.78 (d, 1H, *J* = 12.4 Hz, =CH*H*), 4.94 (d, 2H, *J* = 13.6 Hz, =CH_2), 4.98 (d, 1H, *J* = 12.5 Hz, =C*H*H), 5.17 (d, 1H, *J* = 4.8 Hz, H3), 6.81 (d, 2H, *J* = 7.7 Hz, Ar), 6.97 (t, 1H, *J* = 7.4 Hz, Ar), 7.28 (m, 5H, Ar), 7.46 (d, 2H, *J* = 7.3 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.5 (C=*C*=CH_2), 166.5 (CO), 157.8, 139.6, 134.4, 129.2 (Ar, 2CH), 128.5 (Ar, 2CH), 127.2 (Ar, 3CH), 121.9 (Ar, CH), 115.7 (Ar, 2CH), 113.2 (C=*C*H_2), 102.4, 81.3 (CH, H3), 79.8 (OCH), 78.1 (C=*C*H_2), 58.8 (CH, H4), 55.4 (OMe), 47.8 (NCH_2), 20.6 (Me); IR ($CHCl_3$): ν = 2997, 1946, 1758 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{25}NO_3$ [*M*]$^+$: 375.1834; found: 375.1832.

Allenes **4** were prepared from 3-*O*-(aryl) glucofuranosides through selective removal of the 5,6-*O*-isopropylidene group, oxidation, and carbonyl–allenylation. For the synthesis of related starting glucofuranosides see: N. D. Adhikary and P. Chattopadhyay, *Eur. J. Org. Chem.,* 2011, 7346.

Methoxy Allene (–)-4a. From 150 mg (0.47 mmol) of the corresponding α-allenic alcohol, and after chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave the methoxy allene (–)-**4a** (124 mg, 79%) as a colorless oil; $[\alpha]_D$ = –22.1 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (s, 3H, Me), 1.44 (s, 3H, Me), 1.66 (t, 3H, *J* = 3.0 Hz, Me), 3.08 (s, 3H, OMe), 4.01 (d, 1H, *J* = 9.5 Hz, OCH), 4.23 (dd, 1H, *J* = 9.5, 2.9 Hz, H4), 4.53 (d, 1H, *J* = 3.8 Hz, H2), 4.68 (m, 2H, =CH_2), 4.69 (m, 1H, H3), 5.88

(d, 1H, *J* = 3.8 Hz, H1), 6.91 (t, 1H, *J* = 7.4 Hz, Ar), 6.93 (d, 2H, *J* = 8.0 Hz, Ar), 7.23 (t, 2H, *J* = 7.2 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.6 (C=*C*=CH_2), 157.3, 129.6 (Ar, 2CH), 121.5 (Ar, CH) , 115.5 (Ar, 2CH), 111.9, 105.1 (CH, H1), 95.2, 82.2 (CH, H2), 79.8 (CH, H3), 78.9 (CH, H4), 78.8 (OCH), 74.4 (C=*C*H_2), 56.0 (OMe), 26.8 (Me), 26.3 (Me), 12.6 (Me); IR ($CHCl_3$): ν = 2990, 1941 cm^{-1}; HRMS (ES): calcd for $C_{19}H_{24}O_5$ [*M*]$^+$: 332.1624; found: 332.1624.

Methoxy Allene (–)-4b. From 174 mg (0.52 mmol) of the corresponding α-allenic alcohol, and after chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave the methoxy allene (–)-**4b** (135 mg, 75%) as a colorless oil; $[\alpha]_D$ = –16.9 (*c* = 0.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (t, 3H, *J* = 7,3 Hz, Me), 1.23 (s, 3H, Me), 1.45 (s, 3H, Me), 1.98 (m, 2H, CH_2), 3.08 (s, 3H, OMe), 4.04 (d, 1H, *J* = 9.6 Hz, OCH), 4.26 (dd, 1H, *J* = 9.5, 2.9 Hz, H4), 4.54 (d, 1H, *J* = 3.8 Hz, H2), 4.71 (d, 1H, *J* = 3.1 Hz, H3), 4.81 (m, 2H, =CH_2), 5.88 (d, 1H, *J* = 3.8 Hz, H1), 6.93 (t, 1H, *J* = 7.7 Hz, Ar), 6.94 (d, 2H, *J* = 7.7 Hz, Ar), 7.24 (t, 2H, *J* = 7.1 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.9 (C=*C*=CH_2), 157.3, 129.6 (Ar, 2CH), 121.5 (Ar, CH), 115.5 (Ar, 2CH), 111.9, 105.1 (CH, H1), 102.4, 82.1 (CH, H2), 79.8 (CH, H3), 79.2 (CH, H4), 78.9 (OCH), 76.9 (C=*C*H_2), 56.1 (OMe), 26.8 (Me), 26.4 (Me), 18.8 (CH_2), 12.0 (Me); IR ($CHCl_3$): ν = 2996, 1945 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{26}O_5$ [*M*]$^+$: 346.1780; found: 346.1792.

Methoxy Allene (–)-4c. From 267 mg (0.63 mmol) of the corresponding α-allenic alcohol, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave the methoxy allene (–)-**4c** (221 mg, 80%) as a colorless oil; $[\alpha]_D$ = –27.9 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (s, 3H, Me), 1.36 (s, 3H, Me), 3.13 (s, 3H, OMe), 4.04 (d, 1H, *J* = 11.9 Hz, OC*H*H), 4.13 (d, 1H, *J* = 9.5 Hz, OCH), 4.18 (dt, 1H, *J* = 11.9, 2.3 Hz, OCH*H*), 4.39 (dd, 1H, *J* = 9.5, 3.0 Hz, H4), 4.47 (d, 1H, *J* = 11.9 Hz, OC*H*HAr), 4.52 (d, 1H, *J* = 4.0 Hz, H2), 4.55 (d, 1H, *J* = 12.0 Hz, OCH*H*Ar), 4.72 (d, 1H, *J* = 3.0 Hz, H3), 4.90 (q, 2H, *J* = 11.1 Hz, =CH_2), 5.87 (d, 1H, *J* = 3.8 Hz, H1), 6.92 (t, 1H, *J* = 7.5 Hz, Ar), 6.93 (d, 2H, *J* = 8.5 Hz, Ar), 7.18 (m, 2H, Ar), 7.24 (m, 3H, Ar), 7.29 (t, 2H, *J* = 7.0 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.9 (C=*C*=CH_2), 157.2, 138.3, 129.6 (Ar, 2CH), 128.2 (Ar, 2CH), 127.9 (Ar, 2CH), 127.4 (Ar,CH), 121.5 (Ar,CH), 115.5 (Ar, 2CH), 112.0, 105.2 (CH, H1), 98.6, 82.1 (CH, H2), 80.5 (CH, H3), 79.8 (CH, H4), 77.3 (OCH), 77.1 (C=*C*H_2), 71.7 (O*C*H_2Ar), 67.7 (O*C*H_2), 56.7 (OMe), 26.7 (Me), 26.4 (Me); IR ($CHCl_3$): ν = 3000, 1947 cm^{-1}; HRMS (ES): calcd for $C_{26}H_{30}O_6$ [*M*]$^+$: 438.2042; found: 438.2051.

Methoxy Allene (–)-4d. From 283 mg (0.71 mmol) of the corresponding α-allenic alcohol, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave the methoxy allene (–)-**4d** (225 mg, 77%) as a colorless oil; $[\alpha]_D$ = –22.3 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 3H, Me), 1.52 (s, 3H, Me), 1.73 (t, 3H, *J* = 3.0 Hz, Me), 3.14 (s, 3H, OMe), 4.02 (d, 1H, *J* = 9.5 Hz, OCH), 4.30 (dd, 1H, *J* = 9.5, 3.1 Hz, H4), 4.58 (d, 1H, *J* = 3.8 Hz, H2), 4.73 (d, 1H, *J* = 2.9 Hz, H3), 4.77 (m, 2H, =CH_2), 5.96 (d, 1H, *J* = 3.8 Hz, H1), 6.90 (d, 2H, *J* = 9.1 Hz, Ar), 7.41 (d, 2H, *J* = 9.1 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.7 (C=*C*=CH_2), 156.5, 132.5 (Ar, 2CH), 117.3 (Ar, 2CH), 113.9, 112.1, 105.1 (CH, H1), 95.1, 82.2 (CH, H2), 80.3 (CH, H3), 78.8 (CH, H4), 78.8 (OCH), 74.6 (C=*C*H_2), 56.0 (OMe), 26.8 (Me), 26.4 (Me), 12.6 (Me); IR ($CHCl_3$): ν = 2995, 1945 cm^{-1}; HRMS (ES): calcd for $C_{19}H_{23}BrO_5$ [*M*]$^+$: 410.0729; found: 410.0738.

Methoxy Allene (–)-4e. From 85 mg (0.17 mmol) of the corresponding α-allenic alcohol, and after chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave the methoxy allene (–)-**4e** (85 mg, 99%) as a colorless oil; $[\alpha]_D$ = –12.3 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (s, 3H, Me), 1.36 (s, 3H, Me), 3.11 (s, 3H, OMe), 4.02 (m, 1H, OC*H*H), 4.06 (d, 1H, *J* = 9.6 Hz, OCH), 4.17 (dt, 1H, *J* = 11.8, 2.5 Hz,

OCH*H*), 4.39 (dd, 1H, *J* = 9.5, 3.0 Hz, H4), 4.45 (d, 1H, *J* = 11.8 Hz, OC*H*HAr), 4.47 (d, 1H, *J* = 3.5 Hz, H2), 4.54 (d, 1H, *J* = 11.9 Hz, OCH*H*Ar), 4.65 (d, 1H, *J* = 3.0 Hz, H3), 4.89 (q, 2H, *J* = 11.2 Hz, $=CH_2$), 5.87 (d, 1H, *J* = 3.8 Hz, H1), 6.82 (d, 2H, *J* = 9.1 Hz, Ar), 7.21 (m, 2H, Ar), 7.27 (m, 3H, Ar), 7.33 (d, 2H, *J* = 9.1 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.3 (C=*C*=CH_2), 156.8, 138.7, 132.9 (Ar, 2CH), 128.7 (Ar, 2CH), 128.3 (Ar, 2CH), 127.9 (Ar,CH), 117.6 (Ar, 2CH), 114.2, 112.5, 105.6 (CH, H1), 98.8, 82.5 (CH, H2), 80.9 (CH, H3), 80.7 (CH, H4), 77.3 (OCH), 77.2 (C=*C*H_2), 72.1 (O*C*H_2), 68.1 (O*C*H_2Ar), 57.0 (OMe), 27.1 (Me), 26.8 (Me); IR ($CHCl_3$): ν = 2998, 1947 cm^{-1}; HRMS (ES): calcd for $C_{26}H_{29}BrO_6$ [*M*]$^+$: 516.1184; found: 516.1169.

General Procedure for the Gold-Catalyzed Hydroarylation of Allenyl-Tethered Arenes 1. Preparation of Nine-Membered Fused β-Lactams 3. [$(Ph_3P)AuNTf_2$] (0.05 mmol) was added to a stirred solution of the corresponding allene **1** (1.0 mmol) in 1,2-dichloroethane (13.0 mL) under argon. The resulting mixture was stirred at room temperature (**1a**) or at 110 °C under μwave irradiation (**1b–h**), until disappearance of the starting material (TLC). After filtration through a pad of Celite, the mixture was extracted with ethyl acetate (3 x 5 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure adducts **3**.

Preparation of Diene (–)-2a and Benzocycle (+)-3a. From 80 mg (0.23 mmol) of allene (+)-**1a**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent, 27 mg (34%) of the less polar compound (–)-**2a** and 11 mg (13%) of the more polar compound (+)-**3a** were obtained.

Diene (–)-2a. Colorless oil; $[\alpha]_D$ = –3.5 (*c* = 0.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 6H, *J* = 6.4 Hz, 2Me), 1.74 (m, 1H, CH isobut), 1.84 (d, 3H, *J* = 1.2 Hz, Me), 2.03 (s, 3H, COMe), 2.76 (dd, 1H, *J* = 13.9, 6.7 Hz, NCH*H*), 3.07 (dd, 1H, *J* = 14.0, 7.6 Hz, NC*H*H), 4.64 (dd, 1H, *J* = 9.6, 4.4 Hz, H4), 4.81 (d, 1H, *J* = 2.0 Hz, =CH*H*), 5.03 (d, 1H, *J* = 2.2 Hz, =C*H*H), 5.26 (d, 1H, *J* = 4.5 Hz, H3), 5.67 (d, 1H, *J* = 9.6 Hz, =CH), 6.85 (d, 2H, *J* = 7.7 Hz, Ar), 6.92 (t, 1H, *J* = 7.3 Hz, Ar), 7.18 (t, 2H, *J* = 7.4 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6 (COMe), 165.8 (CO), 157.3, 153.2, 135.3, 129.5 (Ar, 2CH), 122.2 (Ar, CH), 121.0 (=CH), 115.5 (Ar, 2CH), 104.1 (=CH_2), 81.7 (CH, H3), 56.5 (CH, H4), 48.4 (NCH_2), 27.5 (CH isobut), 20.3 (2Me), 13.7 (Me); IR ($CHCl_3$): ν = 1758 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{25}NO_4$ [*M*]$^+$: 343.1784; found: 343.1797.

Benzocycle (+)-3a. Colorless oil; $[\alpha]_D$ = +16.8 (*c* = 0.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (d, 3H, *J* = 6.7 Hz, Me), 0,99 (d, 3H, *J* = 6.7 Hz, Me), 1.80 (t, 3H, *J* = 2.6 Hz, Me), 2.03 (m, 1H, CH isobut), 2.11 (s, 3H, COMe), 2.67 (m, 2H, CH_2Ar), 2.95 (dd, 1H, *J* = 13.7, 6.0 Hz, NCH*H*), 3.32 (dd, 1H, *J* = 13.8, 8.6 Hz, NC*H*H), 4.34 (dd, 1H, *J* = 7.2, 5.1 Hz, H4), 5.26 (m, 1H, OCH), 5.29 (d, 1H, *J* = 5.1 Hz, H3), 7.03 (t, 1H, *J* = 7.3 Hz, =CH), 7.10 (d, 2H, *J* = 7.9 Hz, Ar), 7.30 (t, 2H, *J* = 7.6 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7 (COMe), 166.4 (CO), 157.6, 129.6 (Ar, 2CH), 122.5 (=CH), 122.0 (=C), 115.8 (Ar, 2CH), 115.7, 79.9 (CH, H3), 71.1 (OCH), 57.9 (CH, H4), 49.6 (CH_2 isobut), 27.0 (CH isobut), 22.0 (CH_2Ar), 21.1 (Me), 20.4 (Me), 20.1 (Me), 3.5 (Me); IR ($CHCl_3$): ν = 1757 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{25}NO_4$ [*M*]$^+$: 343.1784; found: 343.1797.

Benzocycle (+)-3b. From 68 mg (0.215 mmol) of allene (+)-**1b**, and after chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave tricycle (+)-**3b** (50 mg, 72%) as a colorless oil; $[\alpha]_D$ = +25.9 (*c* = 0.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, 3H, *J* = 6.7 Hz, Me), 0.98 (d, 3H, *J* = 6.7 Hz, Me), 1.81 (t, 3H, *J* = 2.6 Hz, Me), 2.08 (m, 1H, CH isobut), 2.58 (m, 2H, CH_2Ar), 3.10 (dd, 1H, *J* = 13.6, 6.3 Hz,

NCH*H*), 3.28 (dd, 1H, *J* = 13.6, 8.3 Hz, NC*H*H), 3.47 (s, 3H, OMe), 3.67 (dt, 1H, *J* = 8.4, 4.2 Hz, OCH), 4.12 (dd, 1H, *J* = 8,5, 5.1 Hz, H4), 5.23 (d, 1H, *J* = 5.1 Hz, H3), 7.03 (t, 1H, *J* = 7.3 Hz, =CH), 7.13 (d, 2H, *J* = 7.7 Hz, Ar), 7.31 (m, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2 (CO), 158.1, 130.0 (Ar, 2CH), 122.8 (=CH), 121.0 (=C), 116.3 (Ar, 2CH), 115.7, 80.1 (CH, H3), 79.7 (OCH), 59.6 (CH, H4), 57.4 (OMe), 50.1 (NCH_2), 27.3 (CH isobut), 20.8 (2Me), 20.6 (CH_2Ar), 4.1 (Me); IR ($CHCl_3$): ν = 1756 cm^{-1}; HRMS (ES): calcd for $C_{19}H_{25}NO_3$ $[M]^+$: 315.1834; found: 315.1844.

Benzocycle (+)-3c. From 50 mg (0.132 mmol) of allene (+)-**1c**, and after chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave tricycle (+)-**3c** (30 mg, 60%) as a colorless oil; $[\alpha]_D$ = +24.1 (*c* = 0.4 in $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$): δ = 0.92 (d, 3H, *J* = 6.6 Hz, Me), 0.97 (d, 3H, *J* = 6.6 Hz, Me), 2.08 (m, 1H, CH isobut), 2.78 (dd, 1H, *J* = 17.5, 4.5 Hz, CH*H*Ar), 2.94 (dd, 1H, *J* = 17.5, 4.2 Hz, C*H*HAr), 3.11 (dd, 1H, *J* = 13.6, 6.2 Hz, NCH*H*), 3.32 (dd, 1H, *J* = 13.2, 8.3 Hz, NC*H*H), 3.54 (s, 3H, OMe), 3.81 (dt, 1H, *J* = 8.5, 4.4 Hz, OCH), 4.17 (dd, 1H, *J* = 8.3, 5.1 Hz, H4), 5.27 (d, 1H, *J* = 5.0 Hz, H3), 7.04 (t, 1H, *J* = 7.3 Hz, =CH), 7.16 (d, 2H, *J* = 7.6 Hz, Ar), 7.31 (m, 5H, Ar), 7.41 (m, 2H, Ar); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 166.7 (CO), 157.7, 131.7 (Ar, 2CH) ,129.7 (Ar, 3CH), 128.7, 128.3 (Ar, 2CH), 124.0 (=C), 122.4 (=CH), 115.9 (Ar, 2CH), 115.7, 79.7 (CH, H3), 79.3 (OCH), 59.4 (CH, H4), 57.4 (OMe), 49.7 (NCH_2), 27.0 (CH isobut), 21.4 (CH_2Ar), 20.5 (Me), 20.2 (Me); IR ($CHCl_3$): ν = 1757 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{27}NO_3$ $[M]^+$: 377.1991; found: 377.2001.

Benzocycle (+)-3d. From 50 mg (0.16 mmol) of allene (+)-**1d**, and after chromatography of the residue using hexanes/ethyl acetate (7:1) as eluent gave tricycle (+)-**3d** (30 mg, 58%) as a colorless oil; $[\alpha]_D$ = +28.0 (*c* = 0.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75 (d, 3H, *J* = 2.5 Hz, Me), 2.42 (d, 1H, *J* = 17.4 Hz, CH*H*Ar), 2.61 (d, 1H, *J* = 17.4 Hz, C*H*HAr), 3.28 (s, 3H, OMe), 3.65 (m, 1H, OCH), 4.04 (dd, 1H, *J* = 8,6, 5.1 Hz, H4), 4.46 (d, 1H, *J* = 14.8 Hz, NCH*H*), 4.64 (d, 1H, *J* = 14.8 Hz, NC*H*H), 5.20 (d, 1H, *J* = 5.1 Hz, H3), 7.03 (t, 1H, *J* = 7.3 Hz, =CH), 7.13 (d, 2H, *J* = 8.6 Hz, Ar), 7.31 (m, 4H, Ar), 7.53 (m, 3H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3 (CO), 157.4, 130.0 (Ar, 2CH), 129.02 (Ar, 2CH), 128.8 (Ar, 2CH), 127.9 (Ar, CH), 122.4 (=CH), 121.8 (=C), 116.0 (Ar, 2CH), 115.6, 79.5 (CH, H3), 77.6 (OCH), 59.3 (CH, H4), 57.3 (OMe), 46.3 (NCH_2), 20.6 (CH_2Ar), 14.5 (Me); IR ($CHCl_3$): ν = 1758 cm^{-1}; HRMS (ES): calcd for $C_{22}H_{23}NO_3$ $[M]^+$: 349.1678; found: 349.1671.

Benzocycle (+)-3e. From 44 mg (0.108 mmol) of allene (+)-**1e**, and after chromatography of the residue using hexanes/ethyl acetate (7:1) as eluent gave tricycle (+)-**3e** (30 mg, 69%) as a colorless oil; $[\alpha]_D$ = +16.6 (*c* = 0.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.67 (dd, 1H, *J* = 17.5, 4.5 Hz, CH*H*Ar), 2.88 (dd, 1H, *J* = 17.5, 4.0 Hz, C*H*HAr), 3.37 (s, 3H, OMe), 3.80 (dt, 1H, *J* = 8.6, 4.2 Hz, OCH), 4.09 (dd, 1H, *J* = 8.6, 5.0 Hz, H4), 4.45 (d, 1H, *J* = 14.6 Hz, NCH*H*), 4.71(d, 1H, *J* = 14.8 Hz, NC*H*H), 5.23 (d, 1H, *J* = 5.1 Hz, H3), 7.04 (t, 1H, *J* = 7.3 Hz, =CH), 7.15 (d, 2H, *J* = 7.7 Hz, Ar), 7.29 (m, 6H, Ar), 7.35 (m, 6H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3 (CO), 157.6, 136.1, 131.6 (Ar, 2CH), 129.6 (Ar, 2CH), 128.7 (Ar, 4CH), 128.5 (Ar, 2CH), 128.2 (Ar, 2CH), 127.9, 127.6, 123.4 (=C),122.5 (=CH), 115.9 (Ar, 2CH), 80.0 (CH, H3), 79.1 (OCH), 58.7 (CH, H4), 57.1 (OMe), 46.0 (NCH_2), 21.3 (CH_2Ar); IR ($CHCl_3$): ν = 1758 cm^{-1}; HRMS (ES): calcd for $C_{27}H_{25}NO_3$ $[M]^+$: 411.1834; found: 411.1835.

Benzocycle (+)-3f. From 46 mg (0.16 mmol) of allene (+)-**1f**, and after chromatography of the residue using hexanes/ethyl acetate (7:1) as eluent gave tricycle (+)-**3f** (32 mg, 65%) as a colorless oil; $[\alpha]_D$ = +16.4 (*c* = 0.2 in $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.30 (d, 3H, *J* = 6.7 Hz, Me), 1.39 (d, 3H, *J* = 6.9 Hz, Me), 1.80 (t, 3H, *J* = 2.6 Hz, Me), 2.52 (d, 1H, *J* = 16.9 Hz, CH*H*Ar), 2.71 (d, 1H, *J* = 16.4 Hz, C*H*HAr), 3.48 (s, 3H,

OMe), 3.62 (dt, 1H, *J* = 8.7, 4.0 Hz, OCH), 3.88 (sept, 1H, *J* = 6.7 Hz, NCH), 4.14 (dd, 1H, *J* = 8,8, 5.1 Hz, H4), 5.15 (d, 1H, *J* = 5.1 Hz, H3), 7.02 (t, 1H, *J* = 7.4 Hz, =CH), 7.13 (d, 2H, *J* = 8.0 Hz, Ar), 7.30 (t, 2H, *J* = 7.4 Hz, Ar); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 165.9 (CO), 157.7, 129.5 (Ar, 2CH), 122.3 (=CH), 120.0 (=C), 116.0 (Ar, 2CH), 115.9, 79.3 (CH, H3), 79.1 (OCH), 58.6 (CH, H4), 56.9 (OMe), 46.2 (NCH), 21.2 (Me), 20.1 (Me), 19.8 (CH_2Ar), 3.7 (Me); IR ($CHCl_3$): ν = 1751 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{23}NO_3$ [*M*]$^+$: 301.1678; found: 301.1674.

Benzocycle (+)-3g. From 60 mg (0.165 mmol) of allene (+)-**1g**, and after chromatography of the residue using hexanes/ethyl acetate (7:1) as eluent gave tricycle (+)-**3g** (36 mg, 59%) as a colorless oil; $[\alpha]_D$ = +17.9 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.31 (d, 3H, *J* = 6.7 Hz, Me), 1.39 (d, 3H, *J* = 6.9 Hz, Me), 2.77 (dd, 1H, *J* = 17.7, 4.1 Hz, CH*H*Ar), 2.98 (dd, 1H, *J* = 17.7, 4.0 Hz, C*H*HAr), 3.55 (s, 3H, OMe), 3.76 (dt, 1H, *J* = 8.7, 4.1 Hz, OCH), 3.90 (sept, 1H, *J* = 6.7 Hz, NCH), 4.19 (dd, 1H, *J* = 8.5, 5.2 Hz, H4), 5.19 (d, 1H, *J* = 5.2 Hz, H3), 7.03 (t, 1H, *J* = 7.2 Hz, =CH), 7.15 (d, 2H, *J* = 8.0 Hz, Ar), 7.30 (m, 5H, Ar), 7.41 (m, 2H, Ar); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 165.9 (CO), 157.7, 131.6 (Ar, 2CH) , 129. (Ar, 2CH), 128.2 (Ar, 2CH), 127.9 (Ar, CH), 127.8, 123.4 (=C),122.3 (=CH), 115.9 (Ar, 2CH), 115.8, 79.2 (CH, H3), 79.1 (OCH), 58.7 (CH, H4), 57.1 (OMe), 46.2 (NCH), 21.3 (Me), 20.9 (CH_2Ar), 20.0 (Me); IR ($CHCl_3$): ν = 1752 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{25}NO_3$ [*M*]$^+$: 363.1834; found: 363.1840.

Benzocycle (+)-3h. From 30 mg (0.08 mmol) of allene (+)-**1h**, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave tricycle (+)-**3h** (19 mg, 63%) as a colorless oil; $[\alpha]_D$ = +14.8 (*c* = 0.4 in $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.76 (s, 3H, Me), 2.73 (dd, 1H, *J* = 17.7, 4.7 Hz, CH*H*Ar), 2.91 (dd, 1H, *J* = 17.6, 4.5 Hz, C*H*HAr), 3.52 (s, 3H, OMe), 3.80 (m, 1H, OCH), 3.83 (d, 1H, *J* = 14.9 Hz, NCH*H*), 4.09 (d, 1H, *J* = 15.0 Hz, NC*H*H), 4.16 (dd, 1H, *J* = 7.9, 5.0 Hz, H4), 4.94 (d, 2H, *J* = 13.9 Hz, =CH_2), 5.29 (d, 1H, *J* = 5.1 Hz, H3), 7.04 (t, 1H, *J* = 7.3 Hz, =CH), 7.15 (d, 2H, *J* = 7.7 Hz, Ar), 7.30 (m, 5H, Ar), 7.40 (m, 2H, Ar); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 166.6 (CO), 157.8, 157.7, 139.4, 131.6 (Ar, 2CH), 129.6. (Ar, 2CH), 128.2 (Ar, 2CH), 127.9 (Ar, CH), 123.4 (=C),122.4 (=CH), 118.1, 115.9 (Ar, 2CH), 113.2 (C=*C*H_2), 79.9 (CH, H3), 79.0 (OCH), 59.1 (CH, H4), 57.4 (OMe), 47.8 (NCH_2), 21.5 (CH_2Ar), 20.6 (Me); IR ($CHCl_3$): ν = 1758 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{25}NO_3$ [*M*]$^+$: 375.1834; found: 375.1836.

General Procedure for the Gold-Catalyzed Hydroalkylation of Allenyl-Tethered Arenes 4. Preparation of Cyclopenta[*b*]furans 5. [(Ph_3P)AuNTf_2] (0.05 mmol) was added to a stirred solution of the corresponding allene **4** (1.0 mmol) in 1,2-dichloroethane (13.0 mL) under argon. The resulting mixture was stirred at room temperature until disappearance of the starting material (TLC). After filtration through a pad of Celite, the mixture was extracted with ethyl acetate (3 x 5 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure adducts **5**.

Fused Cyclopentene (+)-5a. From 156 mg (0.47 mmol) of allene (–)-**4a**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave tricycle (+)-**5a** (73 mg, 46%) as a colorless oil; $[\alpha]_D$ = +55.9 (*c* = 0.9 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 3H, Me), 1.53 (s, 3H, Me), 1.88 (s, 3H, Me), 2.19 (s, 3H, Me), 3.35 (s, 3H, OMe), 4.53 (dd, 1H, *J* = 6.7, 2.3 Hz, H4), 5.00 (d, 1H, *J* = 2.5 Hz, H2), 5.09 (d, 1H, *J* = 6.9 Hz, OCH), 6.15 (s, 1H, H1), 6.96 (t, 1H, *J* = 7.3 Hz, Ar), 6.97 (d, 2H, *J* = 7.8 Hz, Ar), 7.24 (m, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9, 147.6, 147.2, 129.3 (Ar, 2CH), 121.4 (Ar, CH) , 116.3 (Ar, 2CH), 114.8, 112.7 (CH, H1), 112.0, 104.3 (CH, H2), 83.7 (CH,

H4), 74.4 (OCH), 55.2 (OMe), 27.6 (Me), 27.2 (Me), 11.4 (Me), 9.8 (Me); IR ($CHCl_3$): ν = 1072 cm^{-1}; HRMS (ES): calcd for $C_{19}H_{24}O_5$ [*M*]$^+$: 315.1624; found: 332.1614.

Fused Cyclopentene (+)-5b. From 126 mg (0.36 mmol) of allene (–)-**4b**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave tricycle (+)-**5b** (46 mg, 34%) as a colorless oil; $[\alpha]_D$ = +33.3 (*c* = 0.2 in $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.07 (t, 3H, *J* = 7,6 Hz, Me), 1.41 (s, 3H, Me), 1.53 (s, 3H, Me), 2.19 (s, 1H, Me), 2.29 (q, 2H, *J* = 9.6 Hz, CH_2), 3.34 (s, 3H, OMe), 4.53 (dd, 1H, *J* = 7.0, 2.5 Hz, H4), 5.00 (d, 1H, *J* = 2.5 Hz, H2), 5.09 (d, 1H, *J* = 6.9 Hz, OCH), 6.20 (s, 1H, H1), 6.94 (t, 1H, *J* = 7.3 Hz, Ar), 6.98 (d, 2H, *J* = 7.7 Hz, Ar), 7.24 (t, 2H, *J* = 7.4 Hz, Ar); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 157.8, 146.9, 146.7, 129.1 (Ar, 2CH), 121.3 (Ar, CH), 121.2, 116.2 (Ar, 2CH), 111.8, 111.0 (CH, H1), 104.2 (CH, H2), 83.4 (CH, H4), 74.4 (OCH), 55.1 (OMe), 27.4 (Me), 27.0 (Me), 17.8 (CH_2), 14.6 (Me), 11.4 (Me); IR ($CHCl_3$): ν = 1074 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{26}O_5$ [*M*]$^+$: 346.1780; found: 346.1777.

Fused Cyclopentene (+)-5c. From 150 mg (0.34 mmol) of allene (–)-**4c**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave tricycle (+)-**5c** (73 mg, 48%) as a colorless oil; $[\alpha]_D$ = +34.9 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 3H, Me), 1.45 (s, 3H, Me), 2.16 (s, 3H, Me), 3.26 (s, 3H, OMe), 4.22 (d, 2H, *J* = 11.9 Hz, OCH_2), 4.35 (m, 2H, OCH_2Ar), 4.47 (dd, 1H, *J* = 6.7, 2.5 Hz, H4), 4.94 (d, 1H, *J* = 2.5 Hz, H2), 5.06. (d, 1H, *J* = 6.7 Hz, OCH), 6.27 (s, 1H, H1), 6.87 (t, 1H, *J* = 7.2 Hz, Ar), 6.89 (d, 2H, *J* = 7.7 Hz, Ar), 7.16 (m, 2H, Ar), 7.22 (m, 3H, Ar), 7.27 (m, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.8, 150.3, 147.9, 138.0, 129.3 (Ar, 2CH), 128.3 (Ar, 2CH), 127.8 (Ar, 2CH), 127.6 (Ar,CH), 121.6 (Ar,CH), 116.3, 116.4 (Ar, 2CH), 112.0, 111.6 (CH, H1), 104.2 (CH, H2), 83.5 (OCH), 79.4 (CH, H4), 71.5 (OCH_2Ar), 63.2 (OCH_2), 55.2 (OMe), 27.6 (Me), 27.2 (Me), 11.9 (Me); IR ($CHCl_3$): ν = 1071 cm^{-1}; HRMS (ES): calcd for $C_{26}H_{30}O_6$ [*M*]$^+$: 438.2042; found: 438.2034.

Fused Cyclopentene (+)-5d. From 118 mg (0.29 mmol) of allene (–)-**4d**, and after chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave tricycle (+)-**5d** (40 mg, 35%) as a colorless oil; $[\alpha]_D$ = +32.1 (*c* = 0.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 3H, Me), 1.52 (s, 3H, Me), 1.88 (s, 3H, Me), 2.18 (s, 3H, Me), 3.33 (s, 3H, OMe), 4.50 (dd, 1H, *J* = 7.1, 2.4 Hz, H4), 4.95 (d, 1H, *J* = 2.3 Hz, H2), 5.01 (d, 1H, *J* = 6.9 Hz, OCH), 6.13 (s, 1H, H1), 6.84 (d, 2H, *J* = 9.1 Hz, Ar), 7.33 (d, 2H, *J* = 9.1 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.0, 148.0, 146.5, 132.2 (Ar, 2CH), 118.3 (Ar, 2CH), 117.2, 113.9, 112.9 (CH, H1), 111.7, 104.5 (CH, H2), 83.5 (CH, H4), 74.9 (OCH), 55.2 (OMe), 27.8 (Me), 26.9 (Me), 11.4 (Me), 9.9 (Me); IR ($CHCl_3$): ν = 1079 cm^{-1}; HRMS (ES): calcd for $C_{19}H_{23}BrO_5$ [*M*]$^+$: 410.0729; found: 410.0744.

Fused Cyclopentene (+)-5e. From 68 mg (0.13 mmol) of allene (–)-**4e**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave tricycle (+)-**5e** (27 mg, 41%) as a colorless oil; $[\alpha]_D$ = +41.5 (*c* = 0.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 (s, 3H, Me), 1.57 (s, 3H, Me), 2.24 (s, 3H, Me), 3.33 (s, 3H, OMe), 4.30 (m, 2H, OCH_2), 4.44 (m, 2H, OCH_2Ar), 4.53 (dd, 1H, *J* = 7.4, 2.4 Hz, H4), 4.98 (d, 1H, *J* = 2.3 Hz, H2), 5.05 (d, 1H, *J* = 7.0 Hz, OCH), 6.34 (s, 1H, H1), 6.85 (d, 2H, *J* = 9.1 Hz, Ar), 7.29 (m, 2H, Ar), 7.32 (m, 3H, Ar), 7.36 (m, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.9, 150.6, 147.5, 138.0, 132.4 (Ar, 2CH), 127.9 (Ar, 2CH), 127.8 (Ar, 2CH), 127.7 (Ar, CH), 118.4 (Ar, 2CH), 117.1, 114.0, 112.2, 111.9 (CH, H1), 104.2 (CH, H2), 83.4 (OCH), 77.5 (CH, H4), 71.6 (OCH_2Ar), 63.2 (OCH_2), 55.2 (OMe), 27.6 (Me), 27.1 (Me), 11.8 (Me); IR ($CHCl_3$): ν = 1074 cm^{-1}; HRMS (ES): calcd for $C_{26}H_{29}BrO_6$ [*M*]$^+$: 516.1148; found: 516.1154.

Computational Details: All the calculations reported in this paper were obtained with the GAUSSIAN 09 suite of programs.[12] Geometry optimizations were performed using the B3LYP[13] hybrid functional in combination with the double-ζ quality plus polarization def2-SVP basis set[14] for all atoms and the Polarizable Continuum Model (PCM, using CH_2Cl_2 as solvent)[15] to take into account solvent effects. This level is denoted PCM(CH_2Cl_2)-B3LYP/def2-SVP. Reactants and products were characterized by frequency calculations,[16] and have positive definite Hessian matrices. Transition structures (TS's) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the Intrinsic Reaction Coordinate (IRC) method.[17] Single point energy calculations were computed using the dispersion-corrected meta-hybrid M06 functional, which has been recommended for transition metal containing species,[18] with the same PCM/def2-SVP combination on the PCM-B3LYP/def2-SVP optimized geometries. This level is denoted PCM(CH_2Cl_2)-M06/def2-SVP//PCM(CH_2Cl_2)-B3LYP/def2-SVP.

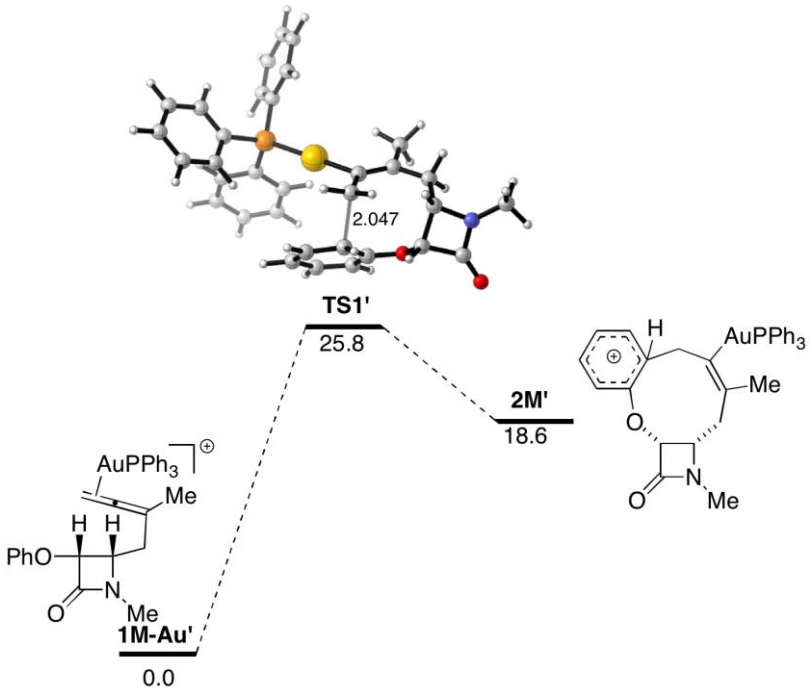


Figure IV.1S. Energy profile for the reaction between allenyl-β-lactam **1M** and [(PPh_3)$AuNTf_2$] catalyst. Relative free energies (ΔG, 298 K) have been computed at the PCM(CH_2Cl_2)-M06/def2-SVP//PCM(CH_2Cl_2)-B3LYP/def2-SVP level.

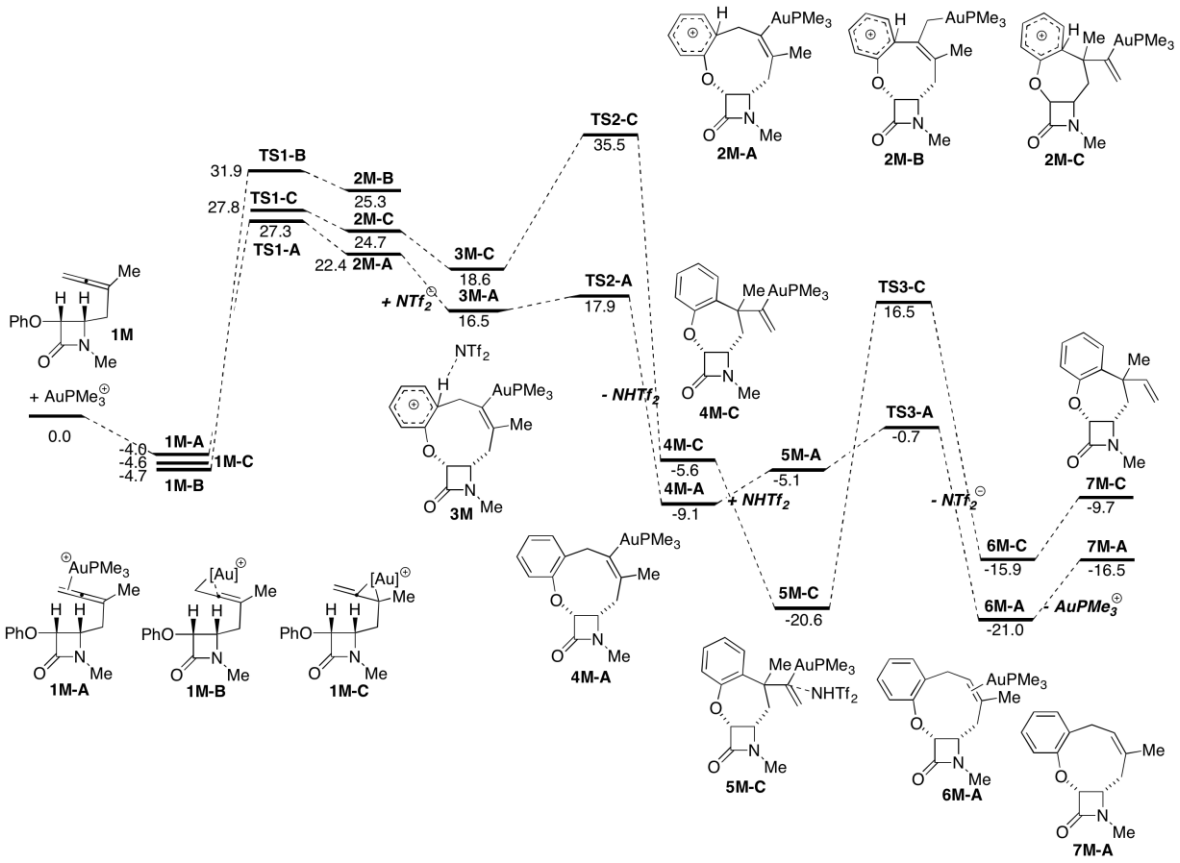


Figure IV.2S. Energy profile for the reaction between allenyl-β-lactam **1M** and [(PMe_3)$AuNTf_2$] catalyst. Relative free energies (ΔG, 298 K) have been computed at the PCM(CH_2Cl_2)-B3LYP/def2-SVP level.

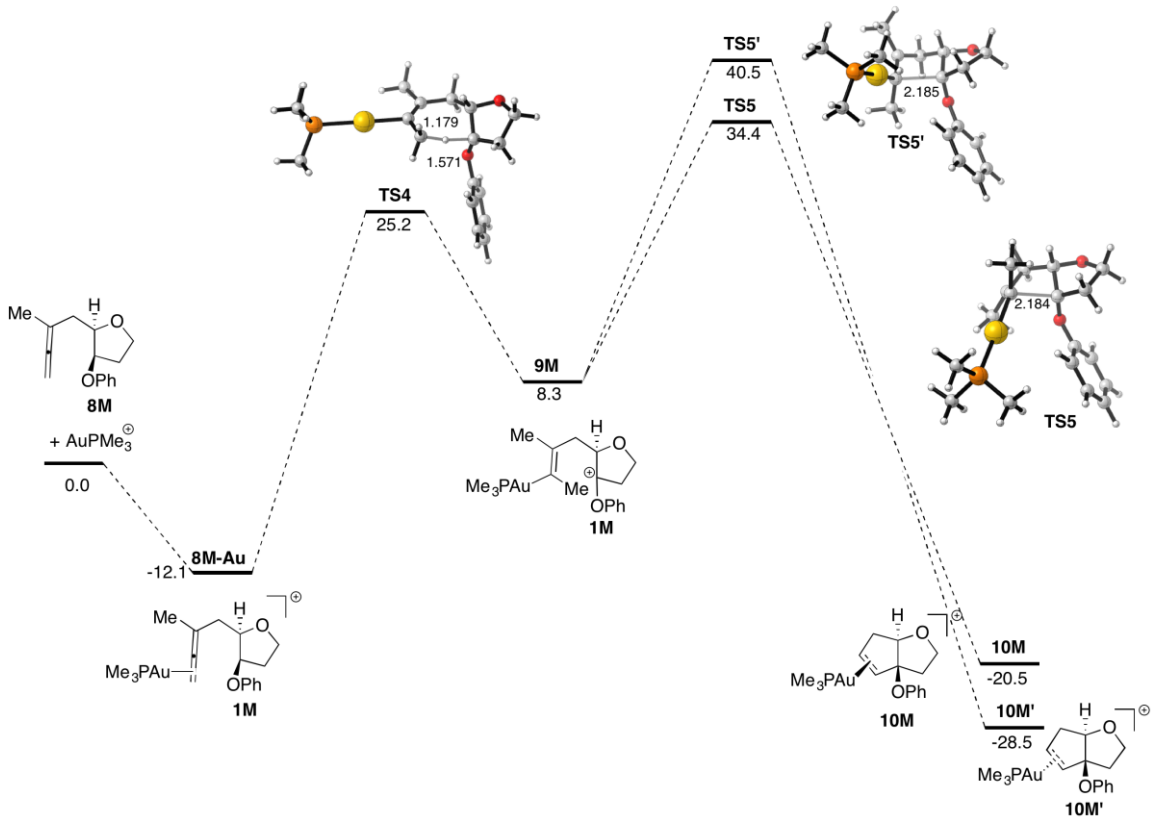


Figure IV.3S. Energy profile for the reaction between allenyl species **8M** and [(PMe_3)AuNTf_2] catalyst. Relative free energies (ΔG, 298 K) have been computed at the PCM(CH_2Cl_2)-M06/def2-SVP//PCM(CH_2Cl_2)-B3LYP/def2-SVP level.

IV.4. Notes and references

1 For a review, see: *(a)* N. Krause and C. Winter, *Chem. Rev.,* 2011, **111**, 1994. For available reports, see: *(b)* W. Kong, C. Fu and S. Ma, *Chem. Eur. J.,* 2011, **17**, 13134; *(c)* B. Alcaide, P. Almendros, J. M. Alonso, M. T. Quirós and P. Gadziński, *Adv. Synth. Catal.,* 2011, **353**, 1871; *(d)* R. M. Zeldin and F. D. Toste, *Chem. Sci.,* 2011, **2**, 1706; *(e)* J. Barluenga, M. Piedrafita, A. Ballesteros, A. L. Suárez-Sobrino and J. M. González, *Chem. Eur. J.,* 2010, **16**, 11827; *(f)* W. Kong, C. Fu and S. Ma, *Eur. J. Org. Chem.,* 2010, 6545; *(g)* D. Weber, M. A. Tarselli and M. R. Gagné, *Angew. Chem. Int. Ed.,* 2009, **48**, 5733; *(h)* D. Weber and M. R. Gagné, *Org. Lett.,* 2009, **11**, 4962; *(i)* M. A. Tarselli and M. R. Gagné, *J. Org. Chem.,* 2008, **73**, 2439; *(j)* C. Park and P. H. Lee, *Org. Lett.,* 2008, **10**, 3359; *(k)* T. Watanabe, S. Ohishi, N. Fujii and H. Ohno, *Org. Lett.,* 2007, **9**, 4821; *(l)* C. Liu and R. A. Widenhoefer, *Org. Lett.,* 2007, **9**, 1935; *(m)* Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Quian and R. A. Widenhoefer, *J. Am. Chem. Soc.,* 2006, **128**, 9066; *(n)* Z. Liu, A. S. Wasmuth and S. G. Nelson, *J. Am. Chem. Soc.,* 2006, **128**, 10352.

2 β-Lactams are not only the most commonly prescribed antibacterial agents, but also exhibit some other biological activities.

3 A. K. Buzas, F. M. Istrate and F. Gagosz, *Org. Lett.,* 2007, **9**, 985.

4 A screening of different gold complexes was undertaken. $AuCl_3$, AuCl, and [(PPh_3)AuOTf] all failed to catalyse this reaction. The cyclizations of allene **1b** using [IPrAuSbF_6] or [IPrAuBF_4] catalysts did not lead to complete consumption of starting **1b**, providing adduct **3b** in very low yield. Change on the nature of the phosphine in the gold pre-catalyst has little effect in the reaction, because replacing [(Ph_3P)AuNTf_2] by [P(*t*Bu)$_2$(*o*-biphenyl)AuNTf_2] did not show any appreciable difference.

5 For a 1,5-hydride shift from benzyl ethers and tetrahydrofurans onto allenes, see: B. Bolte and F. Gagosz, *J. Am. Chem. Soc.,* 2011, **133**, 7696.

6 Biologicaly active heliconols having the 2*H*-cyclopenta[*b*]furan core of fused compounds **5**, have been isolated from natural sources.

7 The barrier energy is reduced to 25.8 kcal/mol when the more realistic $AuPPh_3^+$ catalyst is used (see Figure IV.1S in the IV.3. Experimental Section).

8 See Figure IV.2S in the IV.3. Experimental Section.

9 In sharp contrast, the corresponding proton abstraction and protonolysis reactions in the 7-membered ring formation process proceed with much higher activation barriers ($\Delta G_{a,298}$ = 16.9 and 37.1 kcal/mol). This makes the 7-membered ring formation a non-competitive transformation. See Figure IV.2S in the IV.3. Experimental Section.

10 The easiness of the protonolysis reaction contrasts with related processes whose computed activation barriers are much higher. See: *(a)* B. Alcaide, P. Almendros, T. Martínez del Campo and I. Fernández, *Chem. Commun.,* 2011, **47**, 9054; *(b)* B. Alcaide, P. Almendros, T. Martínez del Campo, E. Soriano and J. L. Marco-Contelles, *Chem. Eur. J.,* 2009, **15**, 1909.

11 Plain values indicate the relative free energies (ΔG, at 298 K) at the PCM(CH_2Cl_2)-M06/def2-SVP//PCM(CH_2Cl_2)-B3LYP/def2-SVP level, whereas values in parentheses

are computed at the PCM(CH_2Cl_2)-B3LYP/def2-SVP level. Bond distances of the transition states are given in angstroms.

12 Gaussian 09, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, Jr. J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

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14 F. Weigend and R. Alhrichs, *Phys. Chem. Chem. Phys*. 2005, **7**, 3297.

15 (a) S. Miertuš, E. Scrocco and J. Tomasi, *Chem. Phys*. 1981, **55**, 117. (b) J. L. Pascual-Ahuir, E. Silla and I. Tuñón, *J. Comp. Chem*. 1994, **15**, 1127. (c) V. Barone and M. Cossi, *J. Phys. Chem. A*, 1998, **102**, 1995.

16 J. W. McIver and A. K. Komornicki, *J. Am. Chem. Soc.* 1972, **94**, 2625.

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V. CAPÍTULO 2

V.1. Iodine recycling via 1,3-migration in iodoindoles under metal catalysis

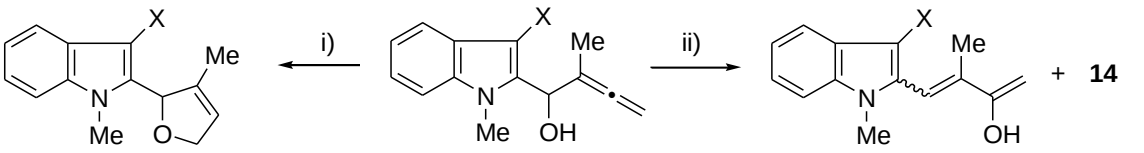
3-Substituted (indol-2-yl)-α-allenols show divergent patterns of reactivity under metal catalysis. An unprecedented intramolecular 1,3-iodine migration is described.

Chem. Commun. **2013**, *49*, 7779

V.2. Communication

Despite that aryl halides are used in many metal-catalysed synthetic developments,[1] low atom economy is a disadvantage because the heteroatom is usually eliminated. A great challenge to be accomplished is the conversion of readily available aryl halides into halogenated products in which the heteroatom is not eliminated but reintegrated in the reaction product.[2] Recently, we have successfully reported metal-catalysed carbocyclizations of 3-unsubstituted (indol-2-yl)-α-allenols for the direct preparation of the relevant carbazole nucleus.[3] We envisioned that different behaviour of indole-tethered allenols might be achieved if the reactive C3-indole position was substituted with an activating group. Herein, we report our findings starting from 3-halo- and 3-phenoxy-(indol-2-yl)-α-allenols **10-13**.

To explore the possibility of a 1,3-heteroatom migration, chloro- and bromoallenes **10** and **11** were initially chosen. Unfortunately, 2,5-dihydrofurans **14**, formed through usual palladium-catalysed oxycyclization reaction,[4] and dienes **15**, formed via gold-catalysed rearrangement, were the only products formed (Scheme V.1). The above experiments suggested that the halide recycling is troublesome.



14a X = Cl (0%)
14b X = Br (8%)

10 X = Cl
11 X = Br

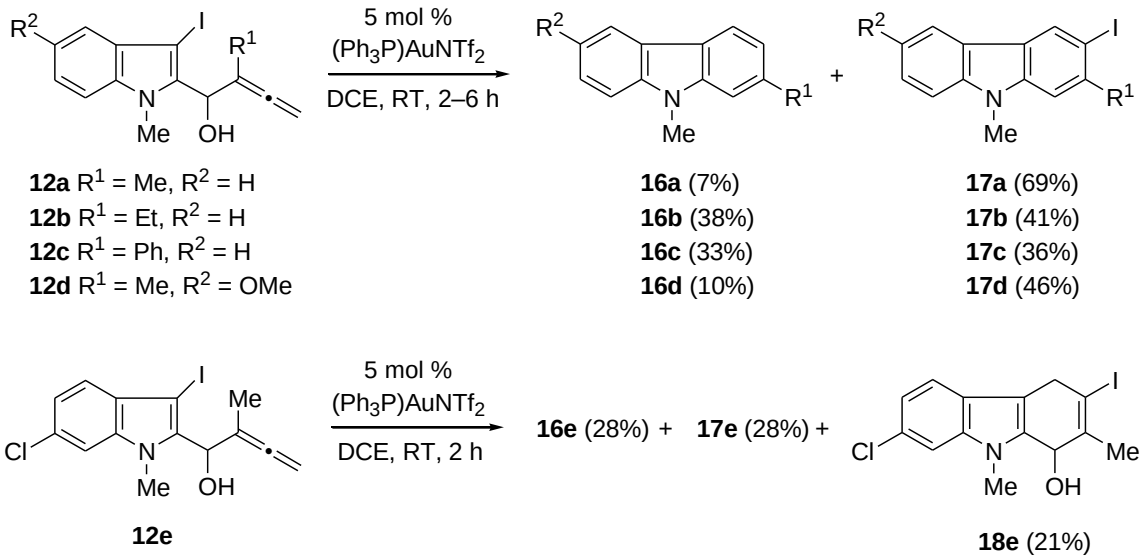
15a X = Cl (20%) **14a** (8%)
15b X = Br (18%) **14b** (2%)

i) $(Ph_3P)_2PdCl_2$ (5 mol %),DMF, RT, 2h
ii) $(Ph_3P)AuNTf_2$ (5 mol %),DCE, RT, 20h

Scheme V.1 Metal-catalysed reactions of 3-chloro/bromo (indol-2-yl)-α-allenols **10** and **11**

We thought that the use of a iodo-alkenyl rather than a Cl(Br)-species to initiate the allene functionalization could make the halogen recycling reaction possible.[2] We first investigated the reactions of allenols **12a–e** bearing a C3-iodosubstituent at the indole nucleus under our previously optimized gold-catalysed conditions. Interestingly, a separable mixture of carbazoles **16a–e** and iodocarbazoles **17a–e** were obtained (Scheme V.2). The iodocyclization of allenol

12a afforded the corresponding 3-iodocarbazole **17a** in 69% yield and carbazole **16a** in 7% yield. Diminished iodocarbazole/carbazole selectivity of ethyl- and phenyl-substituted reactans **12b** and **12c**, were observed with respect to methyl-substituted allenes **12a**, **12d** and **12e**. In addition of the expected carbazole **16e** and iodocarbazole **17e**, 1-hydroxy-3-iododihydrocarbazole **18e** was also formed from chloroderivative **12e**.



Scheme V.2 Synthesis of carbazoles **16**, 3-iodocarbazoles **17**, and 3-iododihydrocarbazole **18e** through carbocyclization/halogen recycling reactions of iodoallenols **12** under gold catalysis.

It should be noted, that in our previous work on metal-catalyzed carbocyclizations 3-unsubstituted (indol-2-yl)-α-allenols, we were not able to form iodocarbazoles **17** by trapping the postulated organometallic intermediate with halogenated reagents.[3a] Considering the versatility of organic iodides in chemical transformations, iodinated carbazoles **17** are potentially interesting building blocks for further manipulation.[5] The structure of 3-iodocarbazole **17d** was unambiguously confirmed with the help of a X-ray diffraction analysis on suitable crystals of this compound (Figure V.1).[6]

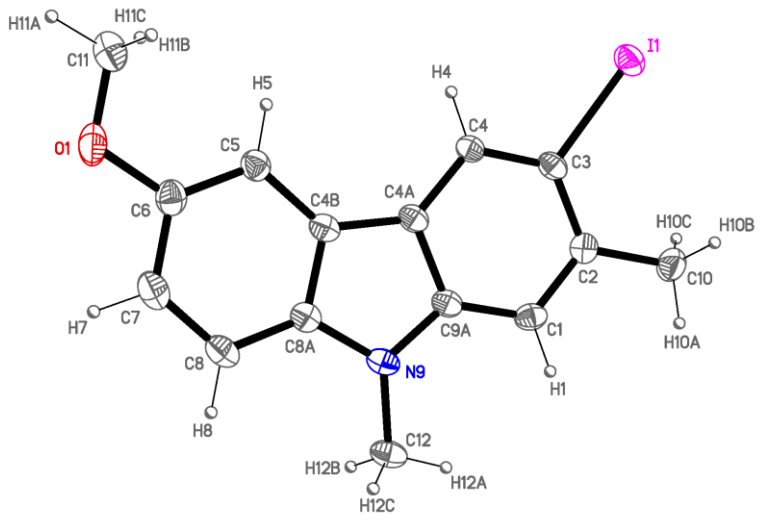
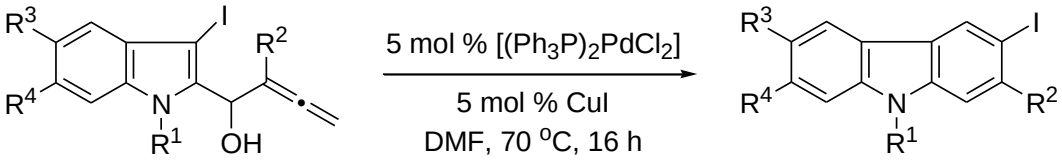


Figure V.1 ORTEP drawing of 3-iodocarbazole **17d**.

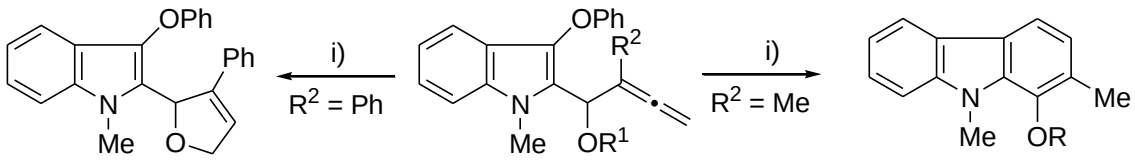
In an attempt to improve the iodocarbocyclization efficiency under related metal-catalysed conditions, we screened a different catalytic system such as $PdCl_2(PPh_3)_2$ on reacting with 3-iodo-(indol-2-yl)-buta-2,3-dienol **12a**. While the Pd-catalysed reaction proceeded with an optimal product distribution (100:0 ratio of the desired 1,3-iodine migration product to the non-iodinated carbazole), the isolated yield of 3-iodocarbazole **17a** was poor (38%). Therefore, we moved to a different catalytic system. Finally, compound **17a** was prepared in acceptable yield (61%) via the reaction of **12a** in the presence of a Pd**–**Cu bimetallic system in DMF. Nicely, indoles **12a**, **12e**, **12f** and **12h**, bearing a methyl substituent on the allene moiety, furnished exclusively 3-iodocarbazoles **17a**, **17e**, **17f** and **17h** (Scheme V.3). Unfortunately, attempts to use phenyl-substituted substrates **12c** and **12g** proved to be unsuccessful for the construction of the corresponding iodocarbazoles, possibly because of both unfavourable steric factors as well as a direct interaction of the π-aromatic system with the metal center from the catalyst. In addition to atom economy and bond-forming efficiency, the above metal-catalysed cases in Scheme V.2 and Scheme V.3, may be considered as examples of the rare recycling of halogen groups via 1,3-halogen migration.[7]



12a R^1 = Me, R^2 = Me, R^3 = R^4 = H — **17a** (61%)
12c R^1 = Me, R^2 = Ph, R^3 = R^4 = H — **17c** (0%)
12e R^1 = Me, R^2 = Me, R^3 = H, R^4 = Cl — **17e** (50%)
12f R^1 = H, R^2 = Me, R^3 = R^4 = H — **17f** (52%)
12g R^1 = H, R^2 = Ph, R^3 = R^4 = H — **17g** (0%)
12h R^1 = H, R^2 = Me, R^3 = OMe, R^4 = H — **17h** (75%)

Scheme V.3 Synthesis of 3-iodocarbazoles **17** through carbocyclization/halogen recycling reactions of iodoallenols **12** under palladium catalysis.

Next, the annulations of 3-phenoxy-(indol-2-yl)-α-allenols **13** were examined (Scheme V.4). To test the reactivity of allenes **13**, we started the initial investigation on the gold-catalysed reaction of allene **13a** under otherwise identical reaction conditions used for its iodocounterpart **12a**. Interestingly, it was found that substrate **13a** was exclusively transformed into the 1-hydroxycarbazole **19a** (Scheme V.4). This interesting transformation can be explained through a gold-catalysed allenic carbocyclization with concomitant hydrodephenoxylation (see below). Thus, it was encountered that the synthesis of structurally interesting 1-oxygenated carbazoles, could be controlled by the C3-substituent on the indole ring in allenes of type **10–13**. Next, 3-phenoxy-(indol-2-yl) allenes **13b** and **13c** were examined in this reaction (Scheme V.4).



14c (46%)

13a R^1 = H, R^2 = Me
13b R^1 = Me, R^2 = Me
13c R^1 = H, R^2 = Ph

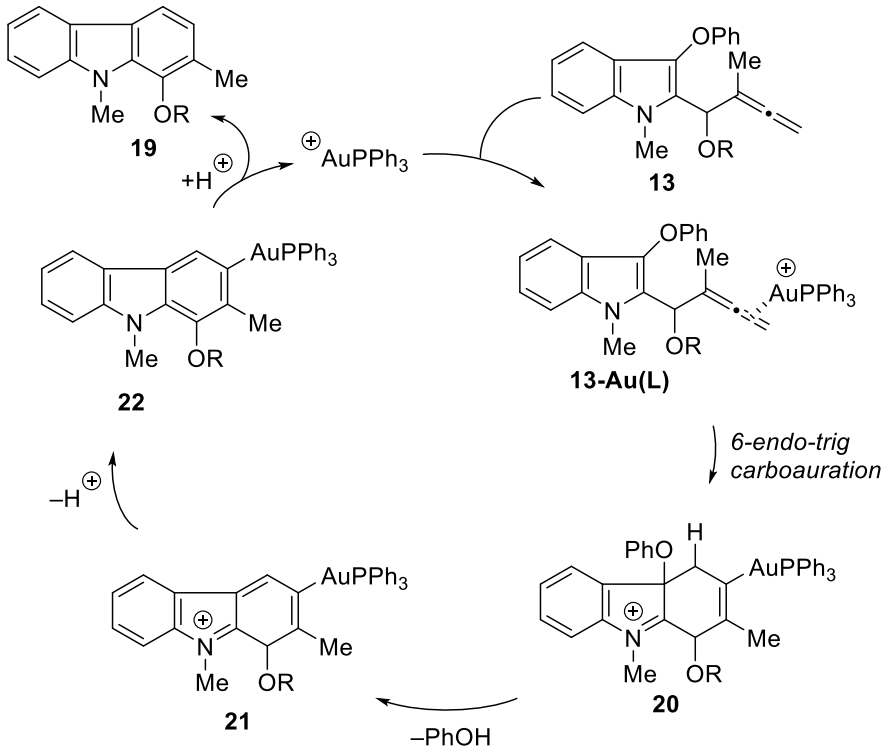
19a R = H (57%)
19b R = Me (51%)

i) $(Ph_3P)AuNTf_2$ (5 mol %),DCE, RT

Scheme V.4 Synthesis of 1-oxygenated carbazoles **19** through carbocyclization/ hydrodephenoxylation reaction of phenoxyallenols **13** under gold catalysis.

Allene **13b** was successfully converted to 1-methoxycarbazole **19b** in fair yield in the presence of the Gagosz' catalyst.[8] On the contrary, phenyl-substituted allene **13c** could not lead to the formation of the corresponding 1-hydroxycarbazole, affording instead the 2,5-dihydrofuran **14c**. Hence, the hydroxy group in phenyl-substituted 3-phenoxy-(indol-2-yl)-α-allenol **13c** exclusively suffers 5-*endo* oxycyclization reaction, instead of 6-*endo* carbocyclization.

A possible pathway[9] for the gold-catalysed generation of 1-oxygenated carbazoles **19** is outlined in Scheme V.5. Initially, the formation of a complex **13**-Au(L) through coordination of the gold salt to the distal allenic double bond may be involved. Species **13**-Au(L) suffers an intramolecular chemo- and regioselective 6-*endo*-trig carbocyclization reaction to produce the auratetrahydrocarbazole **20**.



Scheme V.5 Mechanistic explanation for the Au(I)-catalyzed synthesis of 1-oxygenated carbazoles **19** from phenoxyallenols **13**.

This nucleophilic attack from the C3-indole site occurs as a result of the stability of the intermediate iminium type cation **20**. Next, a phenol elimination[10] step occurs in tricycle **20** through C3–OPh bond cleavage to generate the

dihydrocarbazolium **21**. Aromatization by loss of proton generates neutral species **22**, which followed by protonolysis of the carbon–gold bond afforded 1-oxygenated carbazoles **19** with concurrent regeneration of the gold catalyst (Scheme V.5).

Density functional theory (DFT) calculations have been carried out at the PCM-M06/def2-SVP//B3LYP/def2-SVP level[11] to gain more insight into the reaction mechanism of the above discussed transition metal-catalysed carbocyclization/halogen recycling reactions of iodoallenols **12**. Thus, the corresponding computed reaction profile of the reaction of allenol **12a** and the model catalyst $AuPMe_3^+$ is shown in Figure V.2, which gathers the respective free energies, ΔG_{298}, in dichloroethane solution.

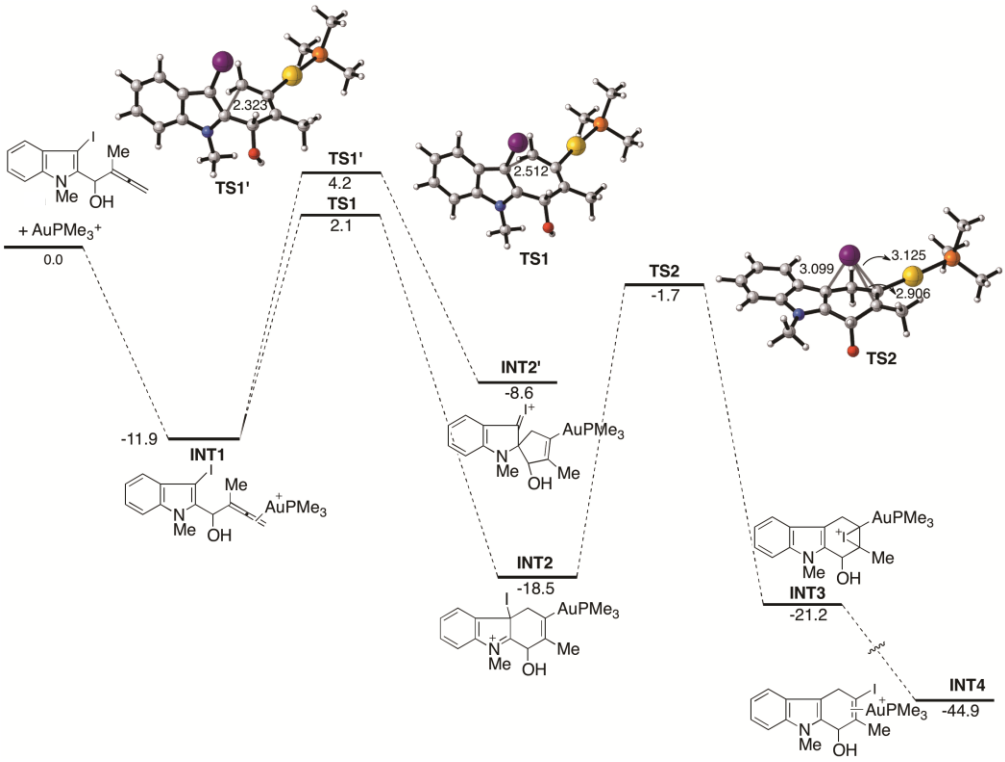


Figure V.2 Computed reaction profile (PCM(dichloroethane)-M06/def2-SVP// B3LYP/def2-SVP level) for the reaction between **12a** and $AuPMe_3^+$. Relative free energies are given in kcal/mol and bond distances in the transition states in angstroms.

The process begins with the exergonic coordination of the catalyst to the distal allenic double bond of **12a** to form intermediate **INT1** ($\Delta G_{R,298}$ = -11.9 kcal mol^{-1}). Then, the nucleophilic attack of the C3-indole position onto the gold(I)-activated double-bond delivers auratetrahydrocarbazole **INT2**. This carbocyclization

reaction occurs through transition state **TS1** with an activation barrier of $\Delta G^{\neq}_{298}$ = 14.0 kcal mol^{-1} in an exergonic transformation ($\Delta G_{R,298}$ = -6.6 kcal mol^{-1}), which is compatible with a process at room temperature. Alternatively, it has been recently suggested that species related to **INT2** may be formed from spiranic species **INT2'** through a 1,2-migration reaction.[12] However, our calculations indicate that the initial formation of **INT2'** via **TS1'**, a saddle point associated with the C2-indole nucleophilic attack, is kinetically and thermodynamically less favoured than the process involving **TS1**, which makes the alternative pathway non-competitive. The origins of this behaviour are found in the well-known activation of the C3-carbon atom by the nitrogen atom of the indole.[13] Once **INT2** is formed, it is transformed into the iodonium species **INT3** through **TS2** (activation barrier of $\Delta G^{\neq}_{298}$ = 16.8 kcal mol^{-1}) in an exergonic process ($\Delta G_{R,298}$ = -2.7 kcal mol^{-1}).

As shown in Figure V.2, **TS2** is associated with the 1,3-migration of the iodine atom to the endocyclic double bond of the adjacent six-membered ring. This step resembles that for typical electrophilic halogen addition to alkenes. Indeed, the computed positive NBO-charge at iodine atom in **INT3** (q = +0.35e) clearly confirms the cyclic-iodonium cation nature of this species. Therefore, this step can be viewed as an unprecedented intramolecular iodine cation addition to a metal-activated double bond. The next step of the transformation involves the liberation of the metal catalyst through formation of the corresponding iododihydrocarbazoles **18** from **INT4**. Subsequent aromatization by dehydration would produce the observed 3-iodocarbazoles **17**. Although the isolation of tricycle **18e** from the reaction of **12e** outlined in Scheme V.2 was fortuitous, the result argues in favour of the suggested reaction mechanism, because an observable intermediate of type **18** was formed.

Finally, we have also investigated why chlorine or bromine substituted allenols **10** and **11** do not undergo a similar 1,3-migration to that found for iodoallenols **12**. As clearly seen in Figure V.3, the computed activation barriers associated with the 1,3-halogen shifts involving chlorine and bromine atoms are much higher than the barrier associated with the migration of iodine ($\Delta G^{\neq}_{298}$ = 29.3 and 23.8 kcal mol^{-1} for Cl and Br, respectively). Therefore, our calculations suggest that the migratory aptitude of halogen atoms in this transition metal-mediated process follows the order I >> Br > Cl, which is in nice agreement with the experimental findings.[14]

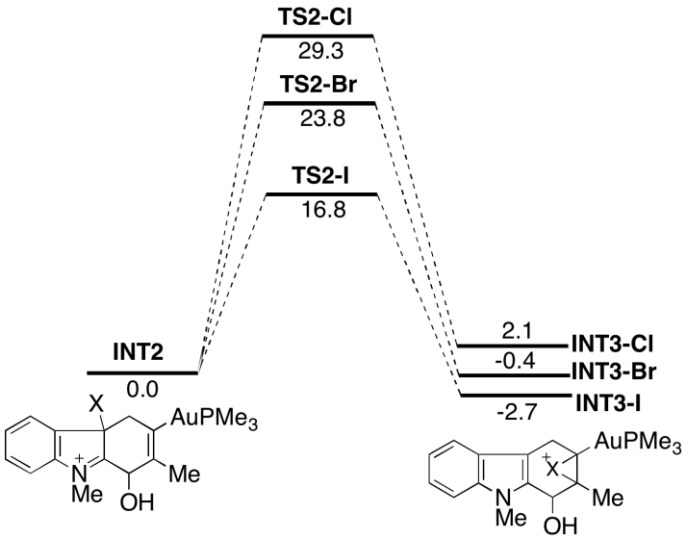


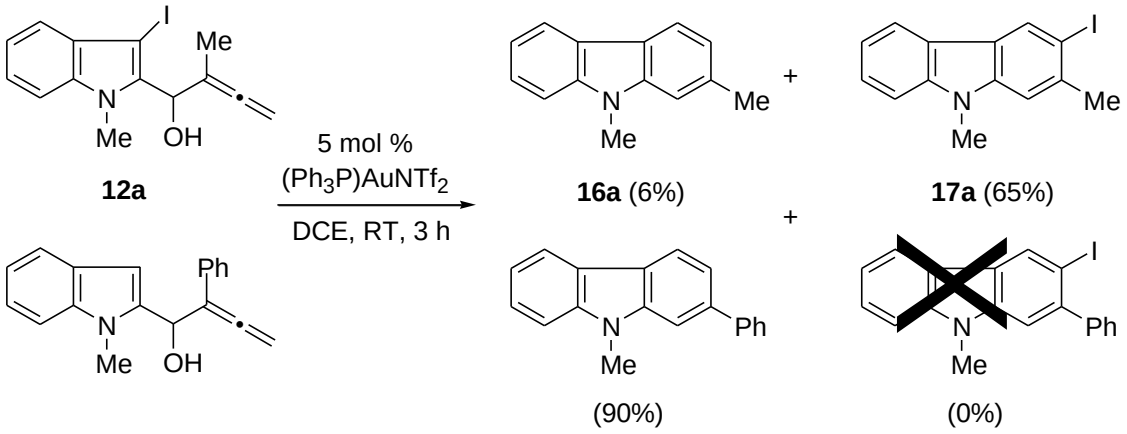
Figure V.3 Comparison of the migratory aptitude of halogen atoms in the proposed 1,3-shift. Relative free energies are given in kcal/mol. All data have been computed at the PCM(dichloroethane)-M06/def2-SVP// B3LYP/def2-SVP levels.

In conclusion, in salient contrast to the reaction of 3-phenoxy-(indol-2-yl) allenes, which were transformed into 1-oxygenated carbazoles, 3-iodo-(indol-2-yl) allenes afforded 3-iodocarbazoles through rare recycling of halogen groups via 1,3-halogen migration. Besides, a computational study suggested the intermediacy of an iodonium cation species formed through an unprecedented intramolecular iodine cation addition to a metal-activated double bond.

V.3. Experimental Section

General Methods: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, Bruker AMX-500, Bruker Avance-300, Varian VRX-300S or Bruker AC-200. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{13}C, 76.9 ppm). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. Specific rotation $[\alpha]_D$ is given in 10^{-1} deg cm^2 g^{-1} at 20 °C, and the concentration (*c*) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

Crossover experiment to test if the iodine transfer is intramolecular or intermolecular: We carried out the reaction of a 1:1 mixture of 1-(3-iodo-1-methyl-1*H*-indol-2-yl)-2-methylbuta-2,3-dien-1-ol (iodoallene **12a**) and 1-(1-methyl-1*H*-indol-2-yl)-2-phenylbuta-2,3-dien-1-ol (same allene as **12a** but replacing *C*-Me for *C*-Ph and without the iodine substituent). In the event, the gold catalyzed treatment of both allenyl-indoles did not show any appreciable formation of the phenylsubstituted iodocarbazole (see Scheme V.S1 in the V.3. Experimental Section); which points to an intramolecular shift of iodine.



Scheme V.S1

Indium-promoted reaction between 3-substituted prop-2-ynyl bromides and 3-functionalized-indole-2-carbaldehydes; general procedure for the synthesis of α-allenic alcohols 10–13. 1-Bromo-2-butyne, 1-bromopent-2-yne, or 1-bromo-3-phenyl-2-propyne (3.0 mmol) was added to a well stirred suspension of the corresponding aldehyde (1.0 mmol) and indium powder (6.0 mmol) in THF/NH_4Cl (aq. sat.) (1:5, 5 mL) at 0 °C. After disappearance of the starting material (TLC) the mixture was extracted with ethyl acetate (3 x 5 mL). The organic extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/hexanes or dichloromethane/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for α-allenic alcohols **10–13** follow.

α-Allenic alcohol 10. From 369 mg (1.91 mmol) of the corresponding aldehyde, and after chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave compound **10** (320 mg, 68%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.61 (dt, 1H, *J* = 7.7, 0.9 Hz, Ar), 7.29 (m, 2H, Ar), 7.19 (td, 1H, *J* = 7.2, 1.8 Hz, Ar), 5.67 (q, 1H, *J* = 3.8 Hz, OCH), 5.02 (m, 2H, $=CH_2$), 3.82 (s, 3H, NMe), 2.45 (d, 1H, *J* = 3.1 Hz, OH),

1.62 (td, 3H, *J* = 3.1, 0.7 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 203.5 (C=*C*=CH_2), 136.5, 132.1, 124.7, 123.0 (Ar, CH), 120.0 (Ar, CH), 118.4 (Ar, CH), 109.2 (Ar, CH), 105.0, 101.5, 79.7 (C=*C*H_2), 65.7 (OCH), 31.0 (NMe), 15.4 (Me); IR ($CHCl_3$): ν = 3417, 1962, 1468, 741 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{14}ClNO$ [*M*]$^+$: 247.0764; found: 247.0756.

α-Allenic alcohol 11. From 160 mg (0.675 mmol) of the corresponding aldehyde, and after chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent gave compound **11** (184 mg, 94%) as a pale orange oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.46 (1H, d, J = 7.7 Hz, CH Ar), 7.20 (2H, m, CH Ar), 7.10 (1H, m, CH Ar), 5.60 (1H, m, CHOH), 4.93 (2H, m, CH=C=CHH), 3.75 (3H, s, NMe), 1.52 (3H, m, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 203.5 (1C, C=C=CHH), 137.4 (1C, C Ar), 133.8 (1C, C Ar), 126.3 (1C, Ar), 123.1 (1C, CH Ar), 120.2 (1C, CH Ar), 119.5 (1C, CH Ar), 109.3 (1C, CH Ar), 101.6 (1C, C Ar), 91.9 (1C, Ar), 79.8 (1C, C=C=CHH), 66.8 (1C, CHOH), 31.2 (1C, Me), 15.5 (1C, Me); IR ($CHCl_3$): ν = 3412, 1965, 1542, 1043 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{14}BrNO$ [*M*]$^+$: 291.0259; found: 291.0270.

α-Allenic alcohol 12a. From 250 mg (0.88 mmol) of the corresponding aldehyde, and after chromatography of the residue using hexanes/ethyl acetate (12:1) as eluent gave compound **12a** (232 mg, 78%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.44 (dt, 1H, *J* = 7.9, 0.9 Hz, Ar), 7.30 (m, 2H, Ar), 7.20 (td, 1H, *J* = 7.9, 3.9 Hz, Ar), 5.66 (td, 1H, *J* = 4.3, 0.8 Hz, OCH), 5.04 (m, 2H, =CH_2), 3.87 (s, 3H, NMe), 2.39 (br s, 1H, OH), 1.62 (td, 3H, *J* = 3.1, 0.7 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 203.5 (C=*C*=CH_2), 138.8, 136.8, 129.5, 123.2 (Ar, CH), 121.6 (Ar, CH), 120.4 (Ar, CH), 109.4 (Ar, CH), 101.8, 79.8 (C=*C*H_2), 68.7 (OCH), 61.0, 31.2 (NMe), 15.6 (Me); IR ($CHCl_3$): ν = 3437, 1961, 1467, 743 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{14}INO$ [*M*]$^+$: 339.0120; found: 339.0133.

α-Allenic alcohol 12b. From 228 mg (0.80 mmol) of the corresponding aldehyde, compound **12b** (254 mg, 90%) was obtained as crude material. Allenol **12b** easily decomposes and was used for next step without purificacion.

α-Allenic alcohol 12c. From 272 mg (0.95 mmol) of the corresponding aldehyde, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **12c** (144 mg, 38%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.44 (m, 3H, Ar), 7.29 (m, 4H, Ar), 7.20 (m, 2H, Ar), 6.30 (t, 1H, *J* = 4.0 Hz, OCH), 5.25 (qd, 2H, *J* = 12.2, 4.0 Hz, =CH_2), 3.91 (s, 3H, NMe), 2.51 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 207.0 (C=*C*=CH_2), 138.6, 137.2, 133.5, 129.6, 128.6 (Ar, 2CH), 127.5 (Ar, CH), 126.9 (Ar, 2CH), 123.2 (Ar, CH), 121.6 (Ar, CH), 120.3 (Ar, CH), 109.4 (Ar, CH), 108.4, 81.4 (C=*C*H_2), 67.2 (OCH), 61.0, 31.5 (NMe); IR ($CHCl_3$): ν = 3452, 1964, 1470, 743 cm^{-1}; HRMS (ES): calcd for $C_{19}H_{16}INO$ [*M*]$^+$: 401.0277; found: 401.0278.

α-Allenic alcohol 12d. From 120 mg (0.38 mmol) of the corresponding aldehyde, and after chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent gave compound **12d** (126 mg, 90%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.18 (d, 1H, *J* = 8.8 Hz, Ar), 6.92 (dd, 1H, *J* = 8.9, 2.5 Hz, Ar), 6.85 (d, 1H, *J* = 2.5 Hz, Ar), 5.62 (t, 1H, *J* = 4.1 Hz, OCH), 5.01 (m, 2H, =CH_2), 3.90 (s, 3H, NMe), 3.83 (s, 3H, OMe), 2.49 (br s, 1H, OH), 1.61 (t, 3H, *J* = 3.1 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 203.5 (C=*C*=CH_2), 154.8, 137.0, 133.8, 129.8, 113.8 (Ar, CH), 110.3 (Ar, CH), 102.7 (Ar, CH), 101.7, 79.7 (C=*C*H_2), 68.7 (OCH), 60.2, 55.9 (OMe), 31.3 (NMe), 15.6 (Me); IR ($CHCl_3$): ν = 3439, 1961, 1488, 1169, 733 cm^{-1}; HRMS (ES): calcd for $C_{15}H_{16}INO_2$ [*M*]$^+$: 369.0226; found: 369.0230.

α-Allenic alcohol 12e. From 225 mg (0.70 mmol) of the corresponding aldehyde, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave compound **12e** (224 mg, 85%) as a pale brown solid; mp 113–114 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.41 (m, 1H, Ar), 7.21 (m, 2H, Ar), 5.62 (t, 1H, *J* = 4.2 Hz, OCH), 5.02 (m, 2H, $=CH_2$), 3.84 (s, 3H, NMe), 2.39 (br s, 1H, OH), 1.61 (t, 3H, *J* = 3.2 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 203.5 ($C=C=CH_2$), 138.2, 137.2, 130.6, 126.2, 123.5 (Ar, CH), 121.0 (Ar, CH), 110.5 (Ar, CH), 101.6, 80.0 ($C=CH_2$), 68.7 (OCH), 59.9, 31.4 (NMe), 15.6 (Me); IR ($CHCl_3$): ν = 3401, 1961, 1470, 1064, 740 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{13}ClINO$ $[M]^+$: 372.9730; found: 372.9741.

α-Allenic alcohol 12f. From 200 mg (0.738 mmol) of the corresponding aldehyde, and after chromatography of the residue using hexanes/ethyl acetate (7:1) as eluent gave compound **12f** (236 mg, 99%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.68 (1H, s, NH), 7.48 (1H, m, CH Ar), 7.38 (1H, m, CH Ar), 7.25 (2H, m, CH Ar), 5.50 (1H, s, C*H*OH), 5.02 (2H, q, *J* = 2.8 Hz, CH=C=C*HH*), 1.69 (3H, t, *J* = 2.8 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 204.8 (1C, C=*C*=CHH), 138.1 (1C, C Ar), 135.6 (1C, C Ar), 130.4 (1C, Ar), 123.3 (1C, CH Ar), 120.9 (1C, CH Ar), 120.7 (1C, CH Ar), 111.3 (1C, CH Ar), 101.4 (1C, C Ar), 78.9 (1C, C=C=*C*HH), 69.3 (1C, CHOH), 58.6 (1C, CI Ar), 14.7 (1C, Me); IR ($CHCl_3$): ν = 3439, 1967, 1542, 1038 cm^{-1}; HRMS (ES): calcd for $C_{13}H_{12}NOI$ $[M]^+$: 324.9964; found: 324.9952.

α-Allenic alcohol 12g. From 150 mg (0.544 mmol) of the corresponding aldehyde, and after chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent gave compound **12g** (180 mg, 70%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.72 (1H, s, NH), 7.46 (3H, m, CH Ar), 7.29 (6H, m, CH Ar), 6.11 (1H, s, C*H*OH), 5.33 (2H, m, CH=C=C*HH*), 2.59 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 207.6 (1C, C=*C*=CHH), 138.3 (1C, C Ar), 135.5 (1C, C Ar), 133.2 (1C, Ar), 130.6 (1C, C Ar), 128.8 (2C, CH Ar), 127.6 (1C, CH Ar), 126.7 (2C, CH Ar), 123.4 (1C, CH Ar), 121.0 (1C, CH Ar), 120.8 (1C, CH Ar), 111.5 (1C, CH Ar), 108.15 (1C, *C*=C=CHH), 81.9 (1C, C=C=*C*HH), 67.4 (1C, CHOH), 59.1 (1C, C-I Ar), 55.8 (1C, OMe); IR ($CHCl_3$): ν = 3495, 1542, 1038 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{14}NOI$ $[M]^+$: 387.0120; found: 387.0140.

α-Allenic alcohol 12h. From 143 mg (0.477 mmol) of the corresponding aldehyde, and after chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent gave compound **12h** (146 mg, 87%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.50 (1H, s, NH), 7.12 (1H, m, CH Ar), 6.81 (2H, m, CH Ar), 5.36 (1H, s, C*H*OH), 4.89 (2H, m, CH=C=C*HH*), 3.81 (3H, s, OMe), 1.57 (3H, t, *J* = 3.2 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 204.9 (1C, C=*C*=CHH), 155.0 (1C, C Ar), 138.6 (1C, C Ar), 130.9 (1C, Ar), 130.5 (1C, C Ar), 113.8 (1C, CH Ar), 112.3 (1C, CH Ar), 102.2 (1C, CH Ar), 101.3 (1C, C=), 78.8 (1C, C=C=*C*HH), 69.3 (1C, CHOH), 58.6 (1C, C-I Ar), 55.8 (1C, OMe), 14.7 (1C, Me); IR ($CHCl_3$): ν = 3552, 1967, 1540, 1038 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{14}NO_2I$ $[M]^+$: 355.0069; found: 355.0077.

α-Allenic alcohol 13a. From 215 mg (0.86 mmol) of the corresponding aldehyde, and after chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave compound **13a** (201 mg, 77%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.35 (d, 1H, *J* = 8.3 Hz, Ar), 7.26 (m, 4H, Ar), 7.02 (m, 4H, Ar), 5.49 (br s, 1H, OCH), 4.88 (m, 2H, $=CH_2$), 3.83 (s, 3H, NMe), 2.46 (d, 1H, *J* = 2.6 Hz, OH), 1.63 (t, 3H, *J* = 2.6 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 204.0 ($C=C=CH_2$), 159.3, 135.3, 131.5, 129.4 (Ar, 2CH), 126.8, 122.5 (Ar, CH), 121.8 (Ar, CH), 119.8, 119.3 (Ar, CH), 118.4 (Ar, CH), 115.5 (Ar, 2CH), 109.2 (Ar, CH), 101.5, 79.1 ($C=CH_2$), 65.3 (OCH), 30.6 (NMe), 15.6 (Me);

IR ($CHCl_3$): ν = 3401, 1961, 1490, 1369, 1216, 740 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{19}NO_2$ $[M]^+$: 305.1416; found: 305.1420.

α-Allenic alcohol 13b. From 175 mg (0.57 mmol) of allenol **13a**, and after chromatography of the residue using hexanes/ethyl acetate (12:1) as eluent gave compound **13b** (79 mg, 43%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 ^oC): δ = 7.37 (d, 1H, *J* = 8.3 Hz, Ar), 7.26 (m, 4H, Ar), 7.00 (m, 4H, Ar), 5.07 (t, 1H, *J* = 3.8 Hz, OCH), 4.75 (m, 2H, $=CH_2$), 3.83 (s, 3H, NMe), 3.30 (s, 3H, OMe), 1.66 (t, 3H, *J* = 3.1 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^oC): δ = 205.5 ($C=C=CH_2$), 159.3, 135.4, 132.9, 129.3 (Ar, 2CH), 125.3, 122.4 (Ar, CH), 121.7 (Ar, CH), 119.7, 119.2 (Ar, CH), 118.3 (Ar, CH), 115. (Ar, 2CH), 109.2 (Ar, CH), 99.3, 76.8 ($C=CH_2$), 74.5 (OCH), 57.1 (OMe), 30.7 (NMe), 16.2 (Me); IR ($CHCl_3$): ν = 1961, 1489, 1369, 1215, 742 cm^{-1}; HRMS (ES): calcd for $C_{21}H_{21}NO_2$ $[M]^+$: 319.1572; found: 319.1564.

α-Allenic alcohol 13c. From 195 mg (0.78 mmol) of the corresponding aldehyde, compound **13c** (244 mg, 85%) was obtained as crude material. Allenol **13c** easily decomposes and was used for next step without purificacion.

Procedure for the palladium-catalyzed reaction of 3-bromo (indol-2-yl)-α-allenol 11. $Pd(PPh_3)_2Cl_2$ (7 mg) was added to a solution of allenol **11** (60 mg, 0.206 mmol) in DMF (2 mL). After total consumption of the starting material (TLC), the mixture was diluted with AcOEt, washed with water, washed with brine, and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure, and the crude mixture was purified on column chromatography (hexanes/AcOEt 10:1). Dihydrofuran **14b** (5 mg, 8%) was isolated from a complicated reaction mixture.

Dihydrofuran 14b. Colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 ^oC): δ = 7.54 (1H, d, *J* = Hz, Ar), 7.27 (2H, m, Ar), 7.17 (1H, m, Ar), 6.19 (1H, m, CH=), 5.75 (1H, m, CHOH), 4.85 (2H, m, CHH), 3.72 (3H, s, NMe), 1.60 (1H, s, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^oC): δ = 136.6 (1C, C Ar), 135.5 (1C, C Ar), 131.9 (1C, Ar), 126.9 (1C, C Ar), 121.9 (1C, CH Ar), 120.3 (1C, CH Ar), 119.3 (1C, CH Ar), 118.5 (1C, CH Ar), 108.0 (1C, CH Ar), 91.3 (1C, C Ar), 81.8 (1C, CH Ar), 73.4 (1C, CHH), 28.4 (1C, NMe), 10.5 (1C, Me); IR ($CHCl_3$): ν = 2850, 1377, 1188, 599 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{14}BrNO$ $[M]^+$: 291.0259; found: 291.0273.

General procedure for the gold-catalyzed reaction of 3-chloro/bromo (indol-2-yl)-α-allenols 10 and 11. $[(Ph_3P)AuNTf_2]$ (0.05 mmol) was added to a stirred solution of the corresponding allenol **10** or **11** (1.0 mmol) in 1,2-dichloroethane (13.0 mL) under argon. The resulting mixture was stirred at room temperature until disappearance of the starting material (TLC). After filtration through a pad of Celite, the mixture was extracted with ethyl acetate (3 x 5 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave adducts **14** and **15**.

Reaction of chloro-allenol 10. From 69 mg (0.28 mmol) of allenol **10**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent, 14 mg (20%) of the less polar compound **15a** and 5 mg (8%) of the more polar compound **14a** were obtained.

Diene 15a. Colorless oil (diastereomeric mixture 60:40); ^1H NMR (300 MHz, $CDCl_3$, 25 ^oC): δ = 7.50 (dt, 0.6H, *J* = 7.7, 1.1 Hz, Ar), 7.44 (d, 1H, *J* = 8.2 Hz, Ar), 7.39 (d, 0.4H, *J* = 8.3 Hz, Ar), 7.22 (m, 1H, Ar), 7.12 (m, 1H, Ar), 7.00 (s, 0.6H, =CH), 6.44 (q, 0.4H, *J* = 1.5 Hz, =CH), 5.84 (d, 0.6H, *J* = 1.6 Hz, =C*H*H), 5.63 (d, 0.6H, *J* = 1.9 Hz, =CH*H*), 5.25 (d,

0.4H, *J* = 1.6 Hz, =C*H*H), 5.17 (d, 0.4H, *J* = 1.6 Hz, =CH*H*), 3.69 (s, 1.8H, NMe), 3.68 (s, 1.2H, NMe), 2.17 (d, 1.2H, *J* = 1.6 Hz, Me), 2.01 (m, 1.8H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 143.1 (1C), 141.4 (1C), 139.5 (1C), 137.4 (M), 136.9 (m), 133.3 (M), 126.2 (m), 126.0 (M), 123.8 (Ar, CH M), 123.4 (Ar, CH m), 121.0 (Ar, CH M), 120.9 (Ar, CH m), 119.4 (Ar, CH M), 118.4 (Ar, CH M), 118.3 (Ar, CH m), 118.2 (Ar, CH m), 118.2 (Ar, CH m), 117.0 (=CH_2 m), 116.2 (=CH_2 M), 111.6 (m), 110.8 (=CH m), 110.7 (=CH M), 31.2 (NMe), 23.2 (Me m), 17.3 (Me M); IR ($CHCl_3$): ν = 1592, 1465, 1326, 741 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{14}ClNO$ [*M*]$^{+}$: 247.0764; found: 247.0760.

Dihydrofuran 14a. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.53 (dt, 1H, *J* = 7.6, 1.0 Hz, Ar), 7.48 (d, 1H, *J* = 8.3 Hz, Ar), 7.27 (td, 1H, *J* = 7.5, 1.2 Hz, Ar), 7.15 (td, 1H, *J* = 7.5, 1.0 Hz, Ar), 6.11 (m, 1H, =CH), 5.87 (m, 1H, OCH), 4.84 (m, 1H, OC*H*H), 4.73 (m, 1H, OCH*H*), 3.75 (s, 3H, NMe), 1.60 (q, 3H, *J* = 1.5 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 136.6, 135.5, 131.9, 127.8, 123.9 (Ar, CH), 123.2 (Ar, CH), 120.9 (Ar, CH), 118.5 (Ar, CH), 110.5 (=CH), 91.8, 82.3 (OCH), 75.5 (OCH_2), 29.8 (NMe), 12.2 (Me); IR ($CHCl_3$): ν = 1739, 1467, 1062, 742 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{14}ClNO$ [*M*]$^{+}$: 247.0764; found: 247.0760.

Reaction of bromo-allenol 11. From 64 mg (0.22 mmol) of allenol **11**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent, 12 mg (18%) of the less polar compound **15b** and 1 mg (2%) of the more polar compound **14b** were obtained.

Diene 15b. Colorless oil (diastereomeric mixture 60:40); ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 8.06 (d, 0.4H, *J* = 7.7 Hz, Ar), 7.98 (d, 0.6H, *J* = 7.9 Hz, Ar), 7.58 (d, 0.6H, *J* = 7.9 Hz, Ar), 7.53 (d, 0.4H, *J* = 7.7 Hz, Ar), 7.46 (td, 0.6H, *J* = 7.7, 1.2 Hz, Ar), 7.40 (t, 0.6H, *J* = 8.0 Hz, Ar), 7.18 (m, 0.4H, Ar), 7.08 (d, 0.4H, *J* = 7.9 Hz, Ar), 6.95 (s, 0.6H, =CH), 6.30 (d, 0.4H, *J* = 1.5 Hz, =CH), 6.13 (d, 0.6H, *J* = 2.0 Hz, =C*H*H), 5.87 (d, 0.6H, *J* = 1.9 Hz, =CH*H*), 5.50 (d, 0.4H, *J* = 1.7 Hz, =C*H*H), 5.46 (d, 0.4H, *J* = 1.9 Hz, =CH*H*), 3.68 (s, 1.8H, NMe), 3.68 (s, 1.2H, NMe), 2.23 (d, 1.2H, *J* = 1.6 Hz, Me), 2.05 (d, 1.8H, *J* = 0.9 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 143.8 (m), 139.9 (M), 136.9 (m), 134.4 (M), 132.7 (C), 129.1 (M), 125.1 (C), 122.9 (Ar, CH M), 122.6 (Ar, CH m), 121.9 (Ar, CH M), 121.0 (=CH_2 m), 120.3 (Ar, CH M), 120.2 (Ar, CH m), 119.9 (=CH_2 M), 119.5 (Ar, CH M), 119.2 (Ar, CH m), 118.7 (C), 117.5 (Ar, CH m), 109.6 (=CH m), 109.4 (=CH M), 108.5 (m), 31.1 (NMe), 23.7 (Me m), 17.2 (Me M); IR ($CHCl_3$): ν = 1602, 1467, 1264, 740 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{14}BrNO$ [*M*]$^{+}$: 291.0259; found: 291.0251.

General procedure for the gold-catalyzed iodine recycling reaction of α-allenols 12a–e. Synthesis of iodocarbazoles 17a–e. [$(Ph_3P)AuNTf_2$] (0.05 mmol) was added to a stirred solution of the corresponding allenol **12** (1.0 mmol) in 1,2-dichloroethane (13.0 mL) under argon. The resulting mixture was stirred at room temperature until disappearance of the starting material (TLC). After filtration through a pad of Celite, the mixture was extracted with ethyl acetate (3 x 5 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure adducts **17**.

Reaction of iodo-allenol 12a. From 122 mg (0.36 mmol) of allenol **12a**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent, 5 mg (7%) of the less polar compound **16a** and 80 mg (69%) of the more polar compound **17a** were obtained.

Carbazole 16a. Described in Alcaide, B.; Almendros, P.; Alonso, J. M.; Quirós, M. T.; Gadziński, P. *Adv. Synth. Catal.* **2011**, *353*, 1871.

Iodocarbazole 17a. Yellow solid; mp 98–99 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ= 8.48 (s, 1H, Ar), 7.98 (d, 1H, *J* = 7.7 Hz, Ar), 7.45 (t, 1H, *J* = 7.1 Hz, Ar), 7.33 (d, 1H, *J* = 8.1 Hz, Ar), 7.24 (s, 1H, Ar), 7.21 (t, 1H, *J* = 7.4 Hz, Ar), 3.76 (s, 3H, NMe), 2.61 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 141.3, 141.0, 137.6, 130.2 (Ar, CH), 125.9 (Ar, CH), 123.1, 121.4, 120.1 (Ar, CH), 119.2 (Ar, CH), 109.3 (Ar, CH), 108.5 (Ar, CH), 88.7, 29.1 (NMe), 29.0 (Me); IR ($CHCl_3$): ν = 1597, 1450, 1253, 743 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{12}IN$ [*M*]$^{+}$: 321.0014; found: 321.0019.

Reaction of iodo-allenol 12b. From 283 mg (0.80 mmol) of allenol **12b**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent, 64 mg (38%) of the less polar compound **16b** and 112 mg (41%) of the more polar compound **17b** were obtained.

Carbazole 16b. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.11 (d, 1H, *J* = 7.7 Hz, Ar), 8.05 (d, 1H, *J* = 7.9 Hz, Ar), 7.50 (t, 1H, *J* = 7.6 Hz, Ar), 7.42 (d, 1H, *J* = 8.0 Hz, Ar), 7.30 (s, 1H, Ar), 7.27 (t, 1H, *J* = 7.6 Hz, Ar), 7.15 (d, 1H, *J* = 8.0 Hz, Ar), 3.88 (s, 3H, NMe), 2.92 (q, 2H, *J* = 7.6 Hz, CH_2), 1.42 (t, 3H, *J* = 7.6 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 142.4, 141.4, 141.0, 125.1 (Ar, CH), 122.8, 120.7, 120.0 (Ar, CH), 119.9 (Ar, CH), 119.3 (Ar, CH), 118.7 (Ar, CH), 108.3 (Ar, CH), 107.4 (Ar, CH), 29.7 (CH_2), 29.0 (NMe), 16.2 (Me); IR ($CHCl_3$): ν = 1603, 1455, 1322, 744, 725 cm^{-1}; HRMS (ES): calcd for $C_{15}H_{15}N$ [*M*]$^{+}$: 209.1204; found: 209.1208.

Iodocarbazole 17b. Pale brown solid; mp 114–115 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.50 (s, 1H, Ar), 7.99 (dd, 1H, *J* = 7.9, 0.8 Hz, Ar), 7.47 (td, 1H, *J* = 8.0, 1.2 Hz, Ar), 7.35 (d, 1H, *J* = 8.1 Hz, Ar), 7.26 (s, 1H, Ar), 7.23 (td, 1H, *J* = 7.9, 1.0 Hz, Ar), 3.80 (s, 3H, NMe), 2.93 (q, 2H, *J* = 7.5 Hz, CH_2), 1.33 (t, 3H, *J* = 7.4 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 143.0, 141.4, 141.1, 130.7 (Ar, CH), 125.9 (Ar, CH), 123.2, 121.4, 120.2 (Ar, CH), 119.2 (Ar, CH), 108.5 (Ar, CH), 108.1 (Ar, CH), 88.0, 34.9 (CH_2), 29.0 (NMe), 15.2 (Me); IR ($CHCl_3$): ν = 1598, 1450, 1252, 742, 723 cm^{-1}; HRMS (ES): calcd for $C_{15}H_{14}IN$ [*M*]$^{+}$: 335.0171; found: 335.0185.

Reaction of iodo-allenol 12c. From 170 mg (0.42 mmol) of allenol **12c**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent, 36 mg (33%) of the less polar compound **16c** and 58 mg (36%) of the more polar compound **17c** were obtained.

Carbazole 16c. Described in Alcaide, B.; Almendros, P.; Alonso, J. M.; Quirós, M. T.; Gadziński, P. *Adv. Synth. Catal.* **2011**, *353*, 1871.

Iodocarbazole 17c. Pale brown solid; mp 124–125 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.64 (s, 1H, Ar), 8.08 (d, 1H, *J* = 7.9 Hz, Ar), 7.52 (t, 1H, *J* = 7.7 Hz, Ar), 7.45 (m, 6H, Ar), 7.38 (s, 1H, Ar), 7.27 (t, 1H, *J* = 7.9 Hz, Ar), 3.83 (s, 3H, NMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 145.2, 143.1, 141.4, 132.6, 130.8 (Ar, CH), 129.7 (Ar, 2CH), 127.8 (Ar, 2CH), 127.5 (Ar, CH), 126.4 (Ar, CH), 123.3, 121.3, 120.5 (Ar, CH), 119.5 (Ar, CH), 110.0 (Ar, CH), 108.7 (Ar, CH), 86.0, 29.1 (NMe), 29.1 (Me); IR ($CHCl_3$): ν = 1596, 1449, 1251, 744, 699 cm^{-1}; HRMS (ES): calcd for $C_{19}H_{14}IN$ [*M*]$^{+}$: 383.0171; found: 383.0187.

Reaction of iodo-allenol 12d. From 98 mg (0.27 mmol) of allenol **12d**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent, 6 mg (10%) of

the less polar compound **16d** and 43 mg (46%) of the more polar compound **17d** were obtained.

Carbazole 16d. Pale brown solid; mp 121–122 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.93 (d, 1H, *J* = 7.7 Hz, Ar), 7.55 (d, 1H, *J* = 2.5 Hz, Ar), 7.28 (d, 1H, *J* = 8.2 Hz, Ar), 7.17 (s, 1H, Ar), 7.09 (dd, 1H, *J* = 8.8, 2.5 Hz, Ar), 7.03 (d, 1H, *J* = 7.9 Hz, Ar), 3.94 (s, 3H, OMe), 3.80 (s, 3H, NMe), 2.57 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 153.5, 141.9, 136.1, 135.8, 123.1, 120.3, 119..9 (Ar, CH), 119.9 (Ar, CH), 115.4 (Ar, CH), 108.9 (Ar, CH), 108.7 (Ar, CH), 103.2 (Ar, CH), 56.1 (OMe), 29.1 (NMe), 22.3 (Me); IR ($CHCl_3$): ν = 1488, 1288, 1206, 804 cm^{-1}; HRMS (ES): calcd for $C_{15}H_{15}NO$ [*M*]$^+$: 225.1154; found: 225.1160.

Iodocarbazole 17d. Pale brown solid; mp 136–137 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.45 (s, 1H, Ar), 7.48 (d, 1H, *J* = 2.5 Hz, Ar), 7.26 (d, 1H, *J* = 8.9 Hz, Ar), 7.25 (s, 1H, Ar), 7.11 (dd, 1H, *J* = 8.9, 2.5 Hz, Ar), 3.93 (s, 3H, OMe), 3.75 (s, 3H, NMe), 2.62 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 153.7, 141.7, 137.5, 136.1, 130.1 (Ar, CH), 122.9, 121.6, 115.0 (Ar, CH), 109.4 (Ar, CH), 109.2 (Ar, CH), 103.0 (Ar, CH), 56.0 (OMe), 29.1 (NMe), 29.0 (Me); IR ($CHCl_3$): ν = 1487, 1289, 1205, 1167, 838 cm^{-1}; HRMS (ES): calcd for $C_{15}H_{14}INO$ [*M*]$^+$: 351.0120; found: 351.0107. X-ray data of **17d**: crystallized from ethyl acetate/*n*-hexane at 20 ºC; $C_{15}H_{14}INO$ (M_r = 351.17); monoclinic; space group = *P2*(1); a = 6.2989(9) Å, b = 11.262(2) Å; c = 9.742(1) Å; α = 90°; β = 103.974(2)°; γ = 90°; V = 674.2(2) Å^3; Z = 2; cd = 1.730 mg m^{-3}; μ = 2.362 mm^{-1}; F(000) = 344. A transparent crystal of 0.18 x 0.14 x 0.05 mm^3 was used. 2303 (R_{int} = 0.0364) independent reflections were collected on a Bruker Smart CCD difractomer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) operating at 50 Kv and 35 mA. Data were collected over a hemisphere of the reciprocal space by combination of three exposure sets. Each exposure of 20s covered 0.3 in ω. The cell parameter were determined and refined by a least-squares fit of all reflections. The first 100 frames were recollected at the end of the data collection to monitor crystal decay, and no appreciable decay was observed. The structure was solved by direct methods and Fourier synthesis. It was refined by full-matrix least-squares procedures on F^2 (SHELXL-97). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in calculated positions and refined riding on the respective carbon atoms. Final R(Rw) values were R^a = 0.0284, $R_{wF}{}^b$ = 0.0721. CCDC-926119 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the www.ccdc.can.ac.uk/deposit (or from The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; Fax (+44)1223-336033; or deposit@cccdc.cam.ac.uk).

Reaction of iodo-allenol 12e. From 192 mg (0.51 mmol) of allenol **12e**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent, 33 mg (28%) of the less polar compound **16e**, 40 mg (21%) of the intermediate polar compound **9e**, and 51 mg (28%) of the more polar compound **17e** were obtained.

Carbazole 16e. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.00 (d, 1H, *J* = 2.0 Hz, Ar), 7.92 (d, 1H, *J* = 7.92 Hz, Ar), 7.39 (dd, 1H, *J* = 8.6, 2.0 Hz, Ar), 7.29 (d, 1H, *J* = 8.6 Hz, Ar), 7.20 (s, 1H, Ar), 7.08 (d, 1H, *J* = 7.9 Hz, Ar), 3.82 (s, 3H, NMe), 2.58 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 141.8, 139.2, 136.6, 125.0 (Ar, CH), 124.1, 123.8, 120.7 (Ar, CH), 120.1 (Ar, CH), 119.6 (Ar, CH), 119.5, 118.7 (Ar, CH), 109.2 (Ar, CH), 108.8 (Ar, CH), 29.0 (NMe), 22.3 (Me); IR ($CHCl_3$): ν = 1467, 1273, 1074, 803 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{12}ClN$ [*M*]$^+$: 229.0658; found: 229.0649.

Iodocarbazole 17e. Orange solid; mp 147–148 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.43 (s, 1H, Ar), 7.93 (d, 1H, *J* = 1.9 Hz, Ar), 7.41 (dd, 1H, *J* = 8.6, 2.0 Hz, Ar), 7.27 (s, 1H, Ar), 7.26 (d, 1H, *J* = 8.6 Hz, Ar), 3.76 (s, 3H, NMe), 2.64 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 141.6, 139.3, 138.5, 130.4 (Ar, CH), 125.8 (Ar, CH), 124.7, 122.4, 122.1, 119.8 (Ar, CH), 109.5 (Ar, CH), 109.4 (Ar, CH), 89.0, 29.1 (NMe), 29.1 (Me); IR ($CHCl_3$): ν = 1488, 1277, 796 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{11}ClIN$ [*M*]$^{+}$: 354.9625; found: 354.9634.

Iododihidrocarbazole 18e. Pale brown solid; mp 116–117 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.44 (m, 1H, Ar), 7.22 (m, 2H, Ar), 6.11 (t, 1H, *J* = 5.0 Hz, OCH), 4.79 (m, 2H, CH_2), 3.68 (s, 3H, NMe), 1.62 (t, 3H, *J* = 1.1 Hz,Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 182.1, 167.5, 140.6, 137.3, 136.0, 130.6, 126.3, 123.9 (Ar, CH), 121.2 (Ar, CH), 110.5 (Ar, CH), 84.5 (OCH), 81.5 (CH_2), 30.5 (NMe), 14.2 (Me); IR ($CHCl_3$): ν = 1469, 1067, 989, 859, 792 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{13}ClINO$ [*M*]$^{+}$: 372.9730; found: 372.9712.

General procedure for the palladium-catalyzed iodine recycling reaction of α-allenols 12a, 12f, 12g, and 12h. Synthesis of iodocarbazoles 17a, 17f, 17g, and 17h. CuI (5 mol%) and $Pd(PPh_3)_2Cl_2$ (5 mol%) were sequentially added to a solution of the corresponding iodoindole **12** (1.0 mmol) in DMF (33 mL). The mixture was heated to 70 ºC, and stirred overnight. After total consumption of the starting material, the mixture was diluted with AcOEt and washed with water, washed with brine and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure, and the crude mixture was purified on column chromatography, yielding analytically pure adducts **17**.

Iodocarbazole 17a. From 100 mg (0.295 mmol) of allenol **12a**, and after chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave compound **17a** (57 mg, 61%) as a yellow solid; mp 98–99 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.48 (s, 1H, Ar), 7.98 (d, 1H, *J* = 7.7 Hz, Ar), 7.45 (t, 1H, *J* = 7.1 Hz, Ar), 7.33 (d, 1H, *J* = 8.1 Hz, Ar), 7.24 (s, 1H, Ar), 7.21 (t, 1H, *J* = 7.4 Hz, Ar), 3.76 (s, 3H, NMe), 2.61 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 141.3, 141.0, 137.6, 130.2 (Ar, CH), 125.9 (Ar, CH), 123.1, 121.4, 120.1 (Ar, CH), 119.2 (Ar, CH), 109.3 (Ar, CH), 108.5 (Ar, CH), 88.7, 29.1 (NMe), 29.0 (Me); IR ($CHCl_3$): ν = 1597, 1450, 1253, 743 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{12}IN$ [*M*]$^{+}$: 321.0014; found: 321.0019.

Iodocarbazole 17e. From 40 mg (0.167 mmol) of allenol **12e**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound **17e** (30 mg, 50%) as an orange solid; mp 147–148 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.43 (s, 1H, Ar), 7.93 (d, 1H, *J* = 1.9 Hz, Ar), 7.41 (dd, 1H, *J* = 8.6, 2.0 Hz, Ar), 7.27 (s, 1H, Ar), 7.26 (d, 1H, *J* = 8.6 Hz, Ar), 3.76 (s, 3H, NMe), 2.64 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 141.6, 139.3, 138.5, 130.4 (Ar, CH), 125.8 (Ar, CH), 124.7, 122.4, 122.1, 119.8 (Ar, CH), 109.5 (Ar, CH), 109.4 (Ar, CH), 89.0, 29.1 (NMe), 29.1 (Me); IR ($CHCl_3$): ν = 1488, 1277, 796 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{11}ClIN$ [*M*]$^{+}$: 354.9625; found: 354.9634.

Iodocarbazole 17f. From 50 mg (0.154 mmol) of allenol **12f**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **17f** (24 mg, 52%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.42 (1H, s, Ar), 7.89 (1H, d, *J* = 8.1 Hz, Ar), 7.87 (1H, s, NH), 7.32 (2H, m, Ar), 7.26 (1H, m, Ar), 7.15 (1H, m, Ar), 2.51 (1H, s, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 139.8 (1C, C Ar), 139.5 (1C, C Ar), 137.9 (1C, C Ar), 130.4 (1C, CH Ar), 126.1 (1C, CH Ar), 123.8 (1C, C Ar), 122.0 (1C, C Ar), 120.2 (1C, CH Ar), 119.8 (1C, CH Ar), 111.3 (1C, CH Ar), 110.6 (1C, CH Ar), 89.4

(1C, C Ar), 28,9 (1C, Me); IR ($CHCl_3$): ν = 1469, 1249, 701 cm^{-1}; HRMS (ES): calcd for $C_{13}H_{10}IN$ $[M]^+$: 306.9858; found: 306.9854.

Iodocarbazole 17h. From 100 mg (0.282 mmol) of allenol **12h**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound **17h** (70 mg, 75%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.36 (1H, s, Ar), 7.72 (1H, s, NH), 7.37 (1H, d, *J* = 2.4 Hz, Ar), 7.20 (2H, d, *J* = 2.9 Hz, Ar), 7.18 (1H, s, Ar), 6.95 (1H, dd, *J* = 8.7, 2.4 Hz, Ar), 3.82 (3H, s, OMe), 2.48 (1H, s, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 154.1 (1C, C Ar), 140.5 (1C, C Ar), 137.7 (1C, Ar), 134.4 (1C, C Ar), 130.3 (1C, CH Ar), 123.8 (1C, C Ar), 122.5 (1C, C Ar), 115.3 (1C, CH Ar), 111.5 (1C, CH Ar), 111.4 (1C, CH Ar), 102.9 (1C, CH Ar), 88.9 (1C, C-I Ar), 56.0 (1C, OMe), 28.9 (1C, Me); IR ($CHCl_3$): ν = 1469, 1249, 701 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{12}INO$ $[M]^+$: 336.9964; found: 336.9955.

General procedure for the gold-catalyzed reaction of 3-phenoxy-(indol-2-yl)-α-allenols 13a–c. Synthesis of 2,5-dihydrofuran 14c and 1-oxygenated carbazoles 19a,b. $[(Ph_3P)AuNTf_2]$ (0.035 mmol) was added to a stirred solution of the corresponding allene **13** (0.7 mmol) in 1,2-dichloroethane (9.0 mL) under argon. The resulting mixture was stirred at room temperature until disappearance of the starting material (TLC). After filtration through a pad of Celite, the mixture was extracted with ethyl acetate (3 x 4 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure adducts **14c** or **19**.

Dihydrofuran 14c. From 285 mg (0.78 mmol) of allene **13c**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **14c** (129 mg, 46%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.35 (m, 3H, Ar), 7.30 (m, 2H, Ar), 7.23 (m, 3H, Ar), 7.20 (m, 2H, Ar), 7.03 (d, 2H, *J* = 7.2 Hz, Ar), 7.02 (m, 1H, Ar), 6.99 (t, 1H, *J* = 7.5 Hz, Ar), 6.63 (td, 1H, *J* = 5.4, 2.3 Hz, =CH), 6.35 (q, 1H, *J* = 2.1 Hz, OCH), 4.91 (d, 2H, *J* = 5.6 Hz, OCH_2), 3.76 (s, 3H, NMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 159.2, 139.4, 135.4, 132.3, 132.2, 129.3 (Ar, 2CH), 128.5 (Ar, 2CH), 128.2, 128.0 (Ar, CH), 126.1 (Ar, 2CH), 123.1 (Ar, CH), 122.5 (Ar, CH), 121.6 (Ar, CH), 119.7, 119.1 (Ar, CH), 118.5 (Ar, CH), 115.6 (Ar, 2CH), 109.1 (=CH), 78.2 (OCH), 75.1 (OCH_2), 29.8 (NMe); IR ($CHCl_3$): ν = 2850, 1469, 1370, 1213, 743 cm^{-1}; HRMS (ES): calcd for $C_{25}H_{21}NO_2$ $[M]^+$: 367.1572; found: 367.1574.

1-Hydroxycarbazole 19a. From 108 mg (0.35 mmol) of allene **13a**, and after chromatography of the residue using hexanes/ethyl acetate (12:1) as eluent gave compound **19a** (43 mg, 57%) as a yellow solid; mp 128–129 ºC; ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.03 (d, 1H, *J* = 7.7 Hz, Ar), 7.61 (d, 1H, *J* = 7.9 Hz, Ar), 7.46 (t, 1H, *J* = 8.1 Hz, Ar), 7.38 (d, 1H, *J* = 8.1 Hz, Ar), 7.21 (t, 1H, *J* = 7.9 Hz, Ar), 6.97 (d, 1H, *J* = 7.9 Hz, Ar), 4.70 (br s, 1H, OH), 4.19 (s, 3H, NMe), 2.45 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 141.7, 140.2, 129.8, 125.3 (Ar, CH), 123.9, 123.0, 121.5 (Ar, CH), 119.9 (Ar, CH), 118.9, 118.7 (Ar, CH), 112.6 (Ar, CH), 108.6 (Ar, CH), 31.9 (NMe), 15.6 (Me); IR ($CHCl_3$): ν = 3425, 1640, 1400, 1264, 734, 702 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{13}NO$ $[M]^+$: 211.0997; found: 211.0998.

1-Methoxycarbazole 19b. From 60 mg (0.19 mmol) of allene **13b**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **19b** (22 mg, 51%) as an orange solid; mp 131–132 ºC; ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.28 (d, 1H, *J* = 7.9 Hz, Ar), 7.48 (t, 1H, *J* = 7.0 Hz, Ar), 7.39 (d, 1H, *J* = 8.0 Hz, Ar), 7.28 (m, 1H, Ar), 7.26 (m, 1H, Ar), 7.10 (d, 1H, *J* = 8.2 Hz, Ar), 4.02 (s, 3H, NMe), 3.84 (s, 3H, OMe), 2.47 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 153.7,

141.5, 140.8, 128.7 (Ar, CH), 125.2 (Ar, CH), 122.7 (Ar, CH), 121.1, 120.3, 119.0 (Ar, CH), 115.5, 108.1 (Ar, CH), 104.3 (Ar, CH), 59.9 (OMe), 29.2 (NMe), 15.1 (Me); IR ($CHCl_3$): ν = 2927, 1471, 1285, 747, 737 cm^{-1}; HRMS (ES): calcd for $C_{15}H_{15}NO$ $[M]^+$: 225.1154; found: 225.1153.

Computational Details: All the calculations reported in this paper were obtained with the GAUSSIAN 09 suite of programs.[15] Electron correlation was partially taken into account using the hybrid functional usually denoted as B3LYP[16] using the double-ζ quality plus polarization def2-SVP basis set[17] for all atoms. Reactants and products were characterized by frequency calculations,[18] and have positive definite Hessian matrices. Transition structures (TS's) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the Intrinsic Reaction Coordinate (IRC) method.[19] Solvents effects were taken into account using the Polarizable Continuum Model (PCM).[20] Single point calculations (PCM-M06/def2-SVP) on the gas-phase optimized geometries were performed to estimate the change in the Gibbs energies in the presence of dichloroethane as solvent using the dispersion corrected M06[21] functional. This level is denoted PCM-M06/def2-SVP//B3LYP/def2-SVP.

V.4. Notes and references

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VI. CAPÍTULO 3

VI.1. Gold as Catalyst for the Hydroarylation and Domino Hydroarylation/N1–C4 Cleavage of β-Lactam-Tethered Allenyl Indoles

Gold-catalyzed hydroarylation reaction of β-lactam-tethered allenyl indoles gives azeto-oxepino[4,5-b]indol-2-ones, tetrahydroazeto-azocino[3,4-b]indol-2-ones, and hexahydroazeto-azepino[3,4-b]indol-2-ones with very high levels of stereo- and regioselectivity; being favored the 7-exo and 8-endo carbocyclization modes by attack of the indole group towards either the internal or terminal allene carbon, respectively. Hydroarylation across the central carbon of the allene moiety has not been detected. The controlled gold-catalyzed annulations allowed the formation of fused β-lactams without harming the sensitive four-membered heterocycle. Besides, a novel gold-catalyzed domino process, namely, the allenic hydroarylation/N1–C4 β-lactam bond breakage to afford dihydro-oxepino[4,5-b]indole-4-carboxamides has been discovered.

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VI.2. Article

VI.2.1. Introduction

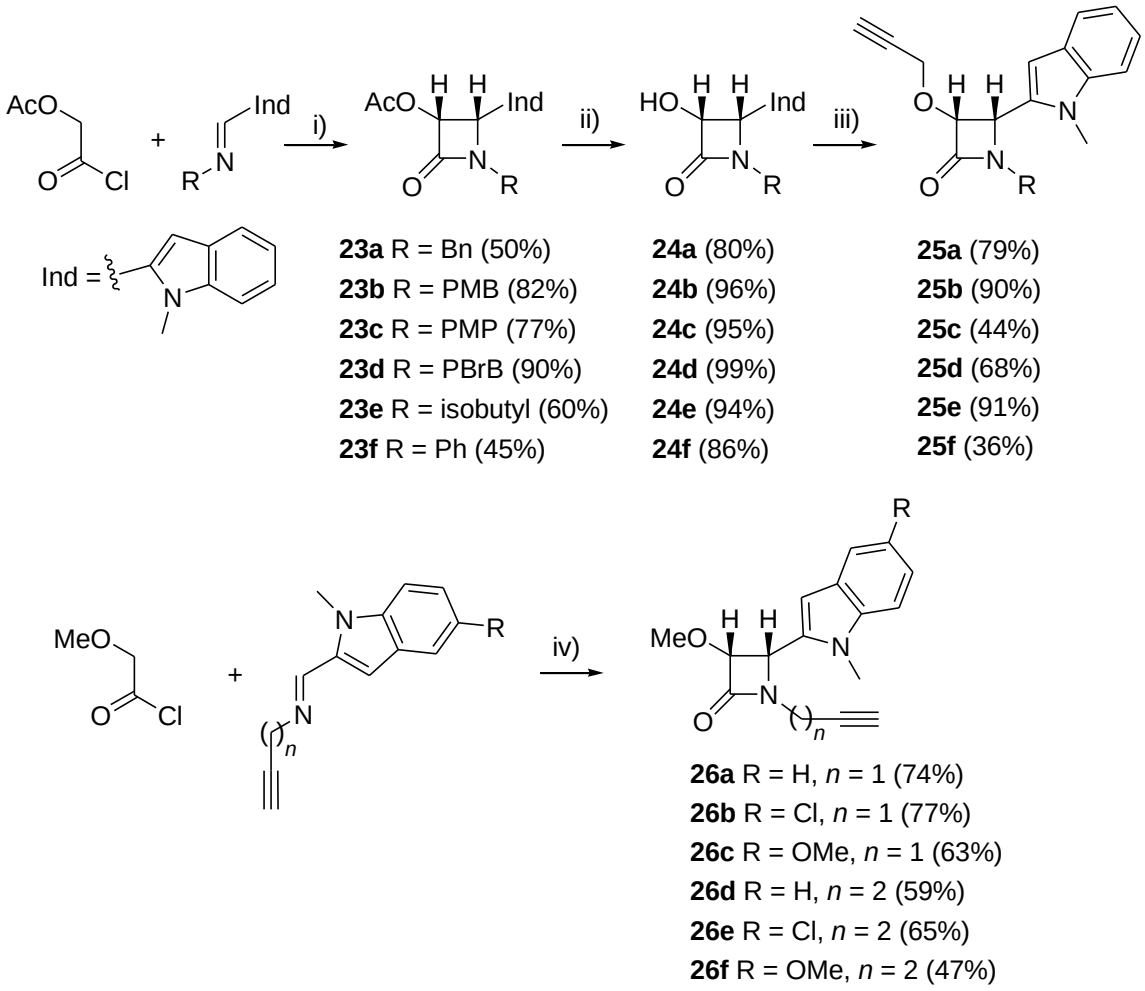
Of the several heterocycles, β-lactams and its derivatives attracted greater attention due to their biological activities such as antibacterial, enzyme inhibitors, neuroprotectors and antitumorals.[1] In addition of the presence of the 2-azetidinone motif in medicinally relevant substances, the β-lactam nucleus is of great importance since 2-azetidinones display relatively high reactivity due to their strained nature, making them versatile intermediates in organic synthesis.[2] Indole derivatives have also received increasing attention in view of their biological and pharmacological activities. In accordance, efforts devoted to the synthesis of both molecular frameworks remain highly desirable.

The direct formation of C–C bonds involving C–H bond cleavage is of great interest because it offers an alternative to the conventional cross-coupling strategies.[3] On the other hand, gold complexes continue to attract considerable interest in the synthetic community due to their powerful soft Lewis acidic nature.[4] In this context, the gold-catalyzed hydroarylation reaction of allenes is an important C–C bond cyclization method.[5] Recently, the gold-catalyzed carbocyclization of allenylindoles has been explored for the preparation of carbazoles, pyridoindoles and cyclopentaindoles.[6] However, the gold-catalyzed intramolecular hydroarylation of indole-tethered allenes to afford medium-sized rings is almost uninvestigated; and just a sole example for the preparation of a seven-membered ring fused indole has been described in literature.[7] We envisioned that β-lactam-tethered allenyl indoles may be effective substrates for this purpose. Herein, we wish to report a synthesis of tetracyclic β-lactam/indole hybrids *via* an allenic hydroarylation approach, together with an unanticipated gold-catalyzed N1–C4 β-lactam bond breakage.

VI.2.2. Results and discussion

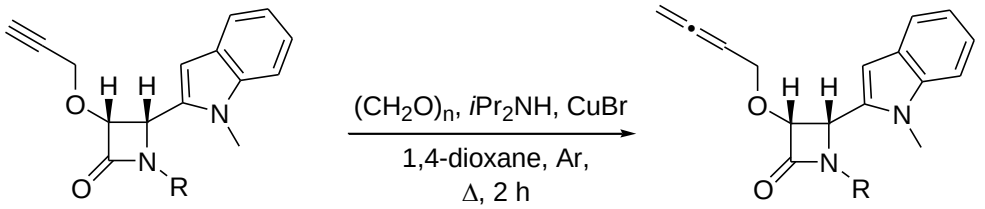
Starting materials, new β-lactam-tethered allenyl indoles **27a–f** and **28a–f** were obtained from 2-azetidinone-tethered alkynyl indoles **25a–f** and **26a–f**. β-

Lactams **23** and **26** (Scheme VI.1) were prepared as single *cis*-diastereoisomers from imines of indole-2-carboxaldehydes through Staudinger reaction with the appropriate alkoxyacetyl chloride in the presence of Et_3N.[8] Transesterification of 3-acetoxy-2-azetidinones **23a–f** with sodium methoxide in methanol gave 3-hydroxy-2-azetidinones **24a–f**, which by treatment with propargyl bromide under basic conditions gave 2-azetidinone-tethered alkynyl indoles **25a–f** (Scheme VI.1). Terminal alkynes **25** and **26** were conveniently converted into allenes **27** and **28** (Scheme VI.2) by treatment with paraformaldehyde in the presence of diisopropylamine and copper(I) bromide (Crabbé reaction).[9]



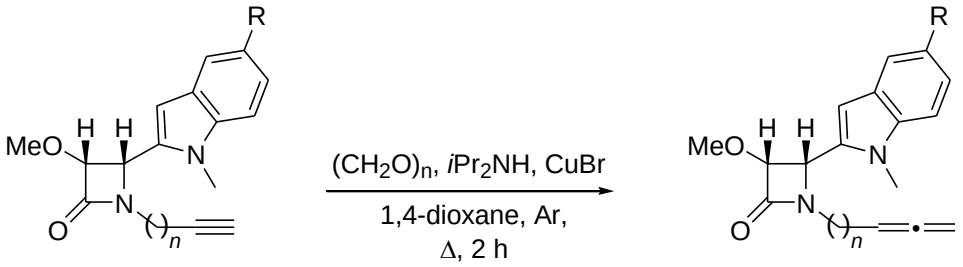
Conditions: i) Et_3N, CH_2Cl_2, rt, 14 h. ii) Sodium methoxide, methanol, 0°C, 30 min. iii) Propargyl bromide, TBAI, NaOH, CH_2Cl_2, H_2O, rt, 14 h. iv) Et_3N, toluene, 80°C, 2 h. PMB = 4-$MeOC_6H_4CH_2$. PMP = 4-$MeOC_6H_4$. PBrB = 4-$BrC_6H_4CH_2$. TBAI = Tetrabutylammonium bromide.

Scheme VI.1. Synthesis of β-lactam-tethered alkynyl indoles **25a–f** and **26a–f**.



25a R = Bn
25b R = PMB
25c R = PMP
25d R = PBrB
25e R = isobutyl
25f R = Ph

27a R = Bn (63%)
27b R = PMB (78%)
27c R = PMP (60%)
27d R = PBrB (50%)
27e R = isobutyl (81%)
27f R = Ph (42%)



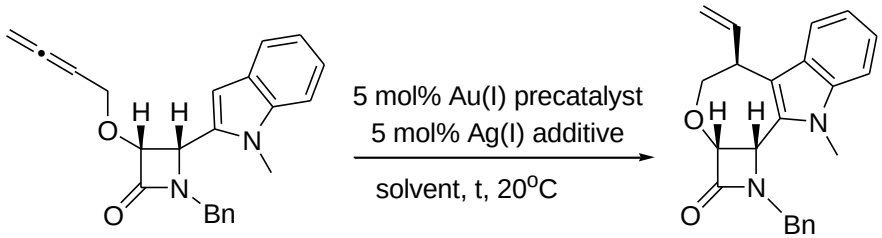
26a R = H, *n* = 1
26b R = Cl, *n* = 1
26c R = OMe, *n* = 1
26d R = H, *n* = 2
26e R = Cl, *n* = 2
26f R = OMe, *n* = 2

28a R = H, *n* = 1 (77%)
28b R = Cl, *n* = 1 (60%)
28c R = OMe, *n* = 1 (47%)
28d R = H, *n* = 2 (46%)
28e R = Cl, *n* = 2 (55%)
28f R = OMe, *n* = 2 (50%)

Scheme VI.2. Preparation of β-lactam-tethered allenyl indoles **27a–f** and **28a–f**.

Initially, we started to evaluate the intramolecular hydroarylation reaction by employing β-lactam-tethered allenyl indole **27a** as model substrate. At the outset, the use of $AuCl_3$ and AuCl were tested, but both failed to catalyze the reaction in the presence or absence of any additive (Table VI.1, entries 1 and 2). Interestingly, when 1-benzyl-3-(buta-2,3-dienyloxy)-4-(1-methyl-1*H*-indol-2-yl)azetidin-2-one **27a** was treated with the system [AuClIPr] (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) (5 mol%)/$AgSbF_6$ (5 mol%) in 1,2-dichloroethane (DCE) at room temperature for 5 h, indolo-oxepino β-lactam **29a** was isolated in 72% yield (Table VI.1, entry 5). The optimal amount of catalyst was established at 5 mol% with a ratio Au(I) salt/Ag(I) salt of 1:1. A lower loading of catalyst had the effect of lowering the conversion for a fixed reaction time (Table VI.1, entry 9). A screening of

solvents (toluene, tetrahydrofuran, 1,4-dioxane) revealed that the reaction is best performed in DCE. Other counter ions has little effect in the reaction, because changing the silver salt to AgOTf, $AgBF_4$, or $AgNTf_2$ also delivered the tetracyclic product but in lower yields (Table VI.1, entries 6–8). Other Au-catalysts were less effective; i.e. low conversion was obtained with $[Au(OTf)PPh_3]$ while Gagosz' catalyst $[(Ph_3P)AuNTf_2]$ leads to considerable decomposition of the starting β-lactam (Table VI.1, entries 3 and 4).



27a **29a**

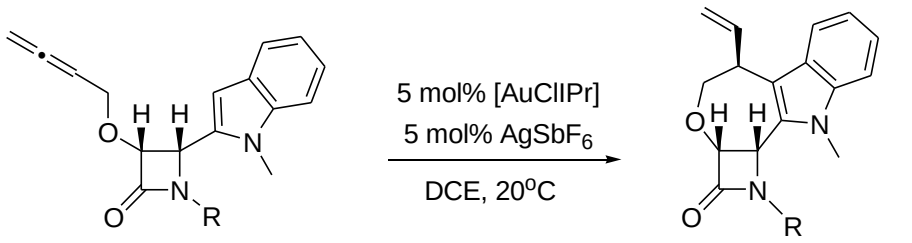
entry	Au(I) salt	Ag(I) salt	solvent/t (h)	yield[a]
1	$AuCl_3$	–	DCE /24	–
2	AuCl	–	DCE/24	–
3	$[AuClPPh_3]$	AgOTf	DCE /24	5
4	$[(Ph_3P)AuNTf_2]$	–	DCE/24	12[b]
5	[AuClIPr]	$AgSbF_6$	DCE/5	72
6	[AuClIPr]	AgOTf	DCE/1.5	43
7	[AuClIPr]	$AgBF_4$	DCE/3	62
8	[AuClIPr]	$AgNTf_2$	DCE/1.5	57
9	[AuClIPr][c]	$AgSbF_6$ [c]	DCE/24	50
10	[AuClIPr]	$AgSbF_6$	dioxane/14	66
11	[AuClIPr]	$AgSbF_6$	toluene/18	60
12	[AuClIPr]	$AgSbF_6$ [d]	DCE/5	69

[a]Yield of pure, isolated product with correct analytical and spectral data. [b]A by-product in which the 2-azetidinone ring disappeared was also detected. [c]1 mol % was used. [d]10 mol % was used.

Table VI.1. Selective hydroarylation reaction of β-lactam-tethered allenyl indole **27a** under modified gold-catalyzed conditions[a]

To ascertain the efficacy and generality of the above catalytic system, various β-lactam-tethered allenyl indoles **27b–e** were treated under the optimized

conditions. The N1-substituents at the β-lactam ring were varied in terms of alkyl and aryl groups. These gold-catalyzed reactions afforded products **29b–e** in yields of 63–89% as exclusive products (Scheme VI.3); regioisomeric adducts not even being detected as trace products. It is obvious from the experiments that in our functionalized systems competitive processes are not operating; being favored the 7-*exo* carbocyclization. Besides, the new stereocenter in tetracycles **29** was created in a totally stereoselective fashion. The stereochemistry of products **29** was unambiguously determined by the NOE analysis of adduct **29d**. Tetracycles **29a–e** can be considered as hybrid scaffolds as combination of the biologically relevant β-lactam, oxepane, and fused indole frameworks.[10] Because most of the reactions were conducted in a 50–100 mg scale, it was desirable to scale-up the procedure. It is worth noting that no obvious loss of yield was observed for adduct **29a** (isolated yield: 70%) when the reaction was carried out on a 500 mg-scale.



27b R = PMB
27c R = PMP
27d R = PBrB
27e R = isobutyl

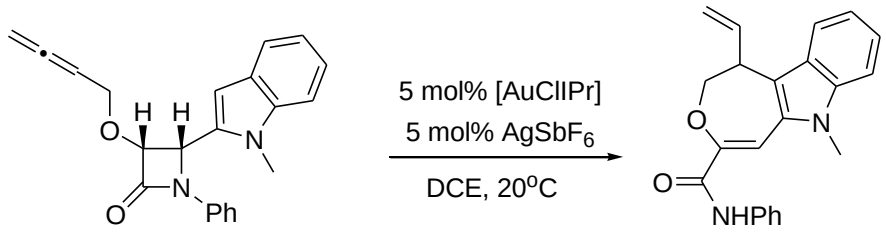
29b R = PMB (68%)
29c R = PMP (63%)
29d R = PBrB (82%)
29e R = isobutyl (89%)

29b: 4.5 h; **29c:** 2.5 h; **29d:** 6.5 h; **29e:** 2 h. PMB = 4-$MeOC_6H_4CH_2$. PMP = 4-$MeOC_6H_4$. PBrB = 4-$BrC_6H_4CH_2$.

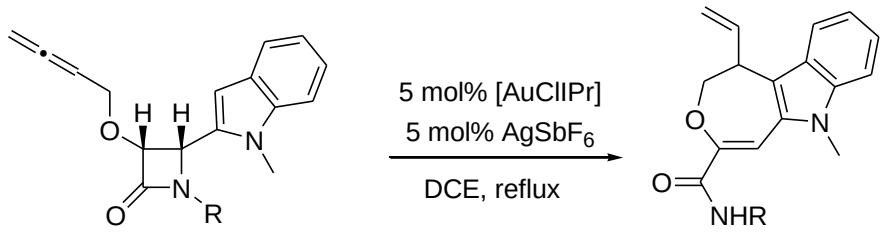
Scheme VI.3. Synthesis of azeto-oxepino[4,5-*b*]indol-2-ones **29b–e** through gold-catalyzed intramolecular hydroarylation reaction of β-lactam-tethered allenyl indoles **27b–e**.

We also performed the above reaction by using the N1-phenyl substrate **27f**. Surprisingly, the reaction does take a different course because the final product **30f**, which was obtained in almost quantitative yield, lacked the β-lactam ring (Scheme VI.4). The formation of dihydro-oxepino[4,5-*b*]indole-4-carboxamide **30f** may imply a selective breakage of the N1–C4 bond of the 2-azetidinone nucleus. We are aware of no report on the metal-catalyzed N1–C4 β-lactam bond cleavage.[11]

Considering the significant effects of reaction temperature on the reactivity of the β-lactam ring,[2] a new reaction conditions were optimized for substrates **27a–e**. Then, the effect of the reaction temperature on the reaction of β-lactam-tethered allenyl indole **27a** was investigated. When the reaction was performed at 40 ^{o}C, it proceeded rapidly and gave a separable mixture (1:1) of tetracycle **29a** and tricycle **30a**. To our delight, reasonable yields and total selectivity in favour of non-β-lactam adduct **30a** was achieved when the gold-catalyzed reaction was performed in DCE at reflux temperature (Scheme VI.4). Under the optimized reaction conditions, the substrate scope was subsequently investigated. Differently substituted β-lactam-tethered allenyl indoles **27b–e** were successfully employed to provide novel fused oxepino-indoles **30b–e** in reasonable yields (Scheme VI.4).



27f **30f** (98%)



27a R = Bn
27b R = PMB
27c R = PMP
27d R = PBrB
27e R = isobutyl

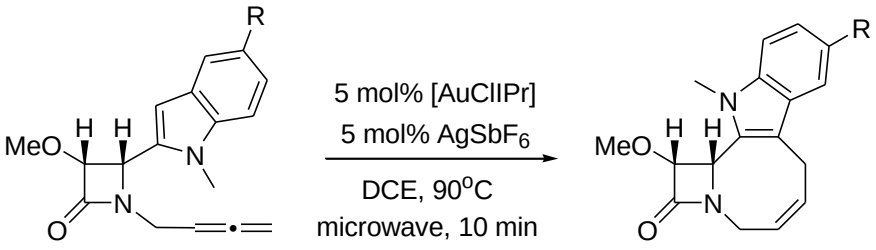
30a R = Bn (60%)
30b R = PMB (53%)
30c R = PMP (67%)
30d R = PBrB (40%)
30e R = isobutyl (58%)

30a: 2 h; **30b:** 2.5 h; **30c:** 2 h; **30d:** 4 h; **30e:** 1.5 h; **30f:** 1.5 h. PMB = 4-MeOC$_6$H$_4$CH$_2$. PMP = 4-MeOC$_6$H$_4$. PBrB = 4-BrC$_6$H$_4$CH$_2$.

Scheme VI.4. Synthesis of 1,6-dihydro-2*H*-oxepino[4,5-*b*]indole-4-carboxamides **30a–f** through gold-catalyzed hydroarylation/N1–C4 β-lactam cleavage of β-lactam-tethered allenyl indoles **27a–f**.

The above cascade sequence tolerated different substituents on the β-lactam nitrogen and could thus provide a good handle in building a larger α-hydroxy amide-appended indole collection. It is possible that traces of $HSbF_6$ are present in the reaction medium. A control experiment that would clarify the participation of $HSbF_6$ as the active catalyst for the β-lactam cleavage was undertaken. When indolo-oxepino β-lactam **29a** was treated with $HSbF_6 \cdot 6H_2O$ with the same catalyst ratio (5 mol%), no product **30a** was obtained; ruling out the participation of the Brønsted acid in the ring-opening process.

To assess the scope of this reaction, the allene moiety was moved from position C3 to N1, as in 1,4-tethered allenylindoles **28**. Attempts of the gold-catalyzed cyclization reaction of compounds **28** failed at room temperature. To our delight, when β-lactam-tethered allenyl indoles **28a–c** were tested as cyclization precursors applying microwave irradiation, after ten minutes it furnished the corresponding tetracycles **31a–c** as the sole isomers (Scheme VI.5).



28a R = H
28b R = Cl
28c R = OMe

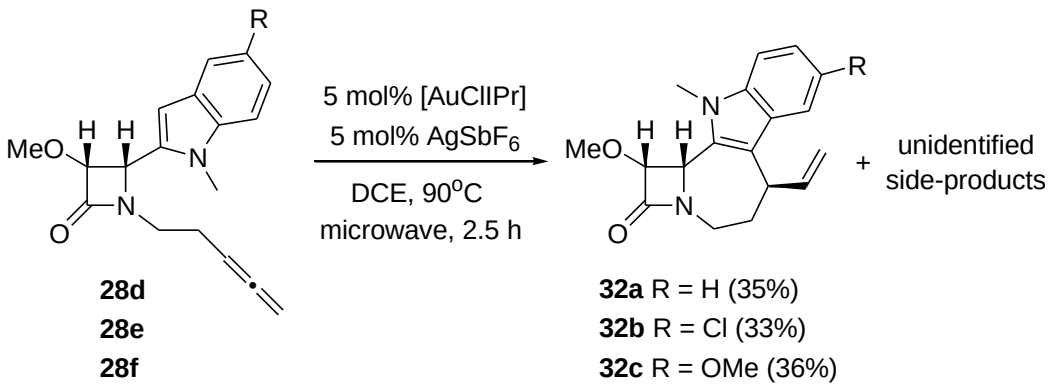
31a R = H (59%)
31b R = Cl (70%)
31c R = OMe (53%)

Scheme VI.5. Synthesis of tetrahydroazeto-azocino[3,4-*b*]indol-2-ones **31a–c** through gold-catalyzed intramolecular hydroarylation reaction of β-lactam-tethered allenyl indoles **28a–c**.

As shown in Scheme VI.4, various substituents with different electronic features at the indole ring showed good reactivity. Both, allenyl indoles **28** bearing electron-donating substituents (MeO) or electron-withdrawing substituents (Cl) worked well to afford the corresponding fused azocines **31**. The formation of tetrahydroazeto-azocino[3,4-*b*]indol-2-ones **31** may be explained through a 8-*endo* carbocyclization of the indole group towards the terminal allene carbon. In this

case, the gold-catalyzed annulations allowed the regioselective formation of fused β-lactams without harming the sensitive four-membered heterocycle.

We also decide to undertake a study of the potential use of more diverse substrates in this novel hydroarylation mode. Thus, β-lactam-tethered allenyl indoles **28d–f** were studied by using the optimum reaction conditions obtained for homologue *N*-allenes **28a–c**. Complete conversion was observed after prolonged exposure, but unidentified side-products from isomerisation or polymerization were detected in the ^{1}H NMR analysis of the crude reaction mixtures. We found a divergent regioselectivity compared with the transformation found with allenes **28a–c**, because tetracycles **32a–c** arising from a 7-*exo* carbocyclization were obtained as major isomers in modest yields (Scheme VI.6). Competing reactions lead to the exclusion of allenyl indoles **28d–f** as efficient substrates.



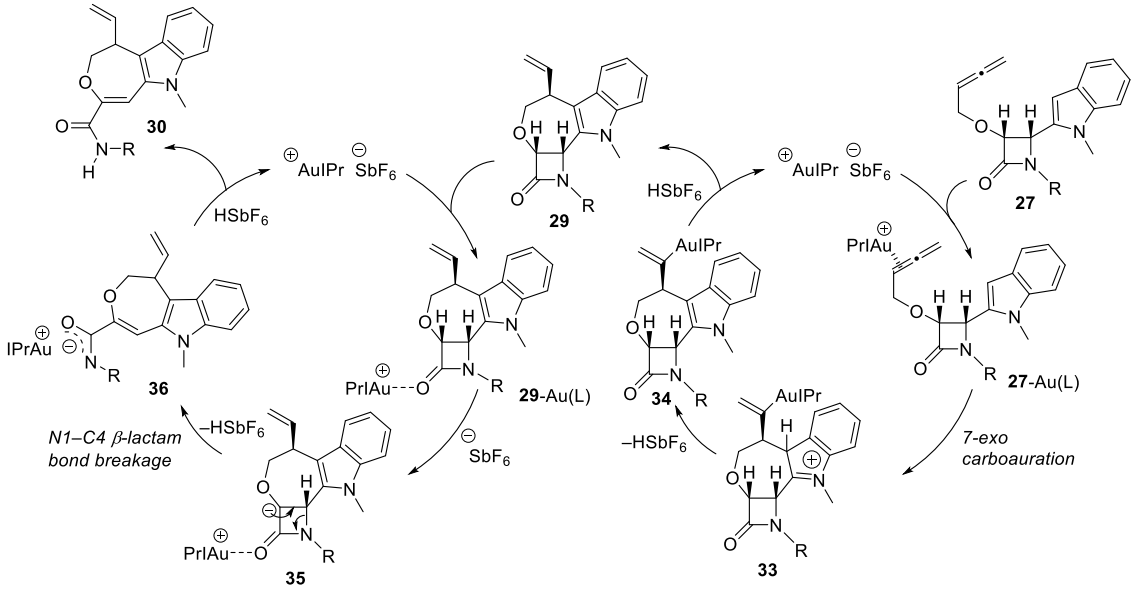
28d
28e
28f

32a R = H (35%)
32b R = Cl (33%)
32c R = OMe (36%)

Scheme VI.6. Synthesis of hexahydroazeto-azepino[3,4-*b*]indol-2-ones **32a–c** through gold-catalyzed intramolecular hydroarylation reaction of β-lactam-tethered allenyl indoles **28d–f**.

A possible pathway for the gold-catalyzed synthesis of dihydro-oxepino[4,5-*b*]indole-4-carboxamides **30** from β-lactam-tethered allenyl indoles **27** may or may not involve a tetracyclic intermediate. The obtention of tetracyclic adducts **29** at room temperature (Scheme VI.3), leads us to propose a mechanism which is illustrated in Scheme VI.7 and occurs through azeto-oxepino[4,5-*b*]indol-2-one species **29**. In order to see if tetracycles **29** are able to rearrange to tricyclic carboxamides **30** under metal-free catalysis, reaction of **29a** was conducted in DCE at reflux temperature for 3 h in the absence of metallic salts. The reaction did not

proceed. In contrast, reaction of **29a** with a catalytic amount of [IPrAuSbF$_6$] under otherwise identical conditions gave the dihydro-oxepino[4,5-*b*]indole-4-carboxamide **30a** in excellent yield. The fact that β-lactam **29a** in the presence of gold(I) was converted into carboxamide **30a** suggests the decisive role of the gold salt in promoting the rearrangement reaction. Probably, initial amide carbonyl coordination to cationic gold in tetracycles **29** is followed by proton abstraction, resulting in the stabilized carbanion **35**. Then, N1–C4 β-lactam bond cleavage should occur to generate the stabilized amide carbanion **36**. Finally, protonolysis leads to the formation of tricycles **30** with concurrent regeneration of the gold catalyst.



Scheme VI.7. Rationalization for the gold-catalyzed hydroarylation/N1–C4 β-lactam cleavage of β-lactam-tethered allenyl indoles **27**.

The first step of the tandem sequence should involve the formation of complex **27**-Au(L) through coordination of the gold salt to the internal allenic double bond. Species **27**-Au(L) undergoes a chemo- and regioselective intramolecular 7-*exo*-trig carbocyclization reaction to produce the auravinyl tetracycle **33**. This nucleophilic attack from the C3-indole site occurs as a result of the stability of the intermediate iminium type cation **33**. Aromatization by loss of proton generates neutral species **34**, which followed by protonolysis of the carbon–gold bond liberates azeto-oxepino[4,5-*b*]indol-2-one species **29**, releasing the gold catalyst

into the first catalytic cycle (Scheme VI.7, right catalytic cycle). Next, tetracycle **29** enters the second catalytic cycle, which is also gold-catalyzed, generating ammonium species **29**-Au(L) by formation of a N–Au bond in an electrophilic fashion. Subsequent proton (H3 at the 2-azetidinone nucleus) abstraction, with concurrent N1–C4 β-lactam bond breakage in species **35** would form the neutral amidogold(I) species **36**. Deauration linked to proton transfer liberates carboxamides **30** with concomitant regeneration of the gold catalyst, closing the second catalytic cycle (Scheme VI.7, left catalytic cycle).

VI.2.3. Conclusion

In conclusion, the present study provides the first insight into the manner in which β-lactam-tethered allenyl indoles undergo carbocyclization under gold catalysis, to afford fused tetracyclic indole-β-lactams having a central seven or eight-membered ring. In addition, a novel domino process, the gold-catalyzed allenic hydroarylation/N1–C4 β-lactam bond breakage was discovered.

VI.3. Experimental Section

General methods: NMR spectra were recorded at 25 ºC on a 300 MHz instrument: ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz). Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{13}C, 76.9 ppm). Low and high resolution mass spectra were taken on a QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES). All reported compounds are racemic. All commercially available compounds were used without further purification.

Staudinger Reaction. General Procedure for the Preparation of Acetoxy β-Lactam-Tethered Indoles 23a–f. To a solution of the corresponding imine (10.4 mmol) in dichloromethane (35 mL) and triethylamine (4.2 mL, 30 mmol) was slowly added acetoxyacetyl chloride (13 mmol) dissolved in dichloromethane (35 mL) at 0ºC under an argon atmosphere and stirring was continued for 14 h at room temperature. Then, 15 mL of $NaHCO_3$ (aq. sat.) were added before being partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (3 x 50 mL), the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/hexanes mixture gave analytically pure compounds **23**.

Acetoxy β-Lactam 23a. From 1.0 g (4.05 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **23a** (711 mg, 50%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.82 (d, 1H, *J* = 7.8 Hz), 7.28 (m, 3H), 7.21 (m, 2H), 7.10 (m, 3H), 6.54 (s, 1H), 5.73 (d, 1H, *J* = 4.4 Hz), 4.91 (d, 1H, *J* = 14.7 Hz), 4.90 (d, 1H, *J* = 4.4 Hz), 3.99 (d, 1H, *J* = 14.8 Hz), 3.48 (s, 3H), 1.67 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 169.6, 164.1, 138.1, 134.3, 131.0, 129.0 (2C), 128.6 (2C), 128.2, 127.2, 122.0, 120.7, 119.8, 109.2, 102.9, 77.5, 53.8, 44.2, 29.6, 20.0; IR ($CHCl_3$, cm^{-1}): ν 2929, 1744, 1216, 734, 699; HRMS (ES): calcd for $C_{21}H_{20}N_2O_3$ $[M]^+$: 348.1474; found: 348.1486.

Acetoxy β-Lactam 23b. From 746 mg (2.68 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **23b** (825 mg, 82%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.63 (d, 1H, *J* = 7.9 Hz), 7.28 (m, 2H), 7.14 (t, 1H, *J* = 7.3 Hz), 7.07 (d, 2H, *J* = 8.6 Hz), 6.84 (d, 2H, *J* = 8.6 Hz), 6.58 (s, 1H), 5.76 (d, 1H, *J* = 4.4 Hz), 4.93 (d, 1H, *J* = 4.4 Hz), 4.89 (d, 1H, *J* = 14.7 Hz), 3.89 (d, 1H, *J* = 14.7 Hz), 3.80 (s, 3H), 3.54 (s, 3H), 1.71 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 169.6, 164.0, 159.5, 138.0, 131.1, 129.9 (2C), 127.2, 126.2, 122.0, 120.7, 119.8, 114.3 (2C), 109.2, 102.9, 77.4, 55.3, 53.6, 43.6, 29.7, 20.0; IR ($CHCl_3$, cm^{-1}): ν 2923, 1753, 1220, 731; HRMS (ES): calcd for $C_{22}H_{22}N_2O_4$ $[M]^+$: 378.1580; found: 378.1574.

Acetoxy β-Lactam 23c. From 917 mg (3.47 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **23c** (965 mg, 77%) as a colorless solid; mp 150–151 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.55 (d, 1H, *J* = 7.9 Hz), 7.33 (m, 1H), 7.32 (d, 2H, *J* = 9.1 Hz), 7.25 (t, 1H, *J* = 7.5 Hz), 7.11 (t, 1H, *J* = 7.4 Hz), 6.81 (d, 2H, *J* = 9.1 Hz), 6.52 (s, 1H), 6.01 (d, 1H, *J* = 4.7 Hz), 5.58 (d, 1H, *J* = 4.7 Hz), 3.78 (s, 3H), 3.76 (s, 3H), 1.74 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 169.6, 160.9, 156.7, 138.2, 130.5, 130.0, 127.1, 122.1, 120.8, 119.8, 118.9 (2C), 114.4 (2C), 109.1, 103.8, 76.5, 55.4 (2C), 30.1, 20.0; IR ($CHCl_3$, cm^{-1}): ν 2923, 1745, 1225, 733; HRMS (ES): calcd for $C_{21}H_{20}N_2O_4$ $[M]^+$: 364.1423; found: 364.1418.

Acetoxy β-Lactam 23d. From 1.25 g (3.81 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave compound **23d** (1.46 g, 90%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.63 (d, 1H, *J* = 7.8 Hz), 7.46 (d, 2H, *J* = 8.4 Hz), 7.32 (d, 1H, *J* = 7.8 Hz), 7.26 (td, 1H, *J* = 8.2, 1.2 Hz), 7.15 (td, 1H, *J* = 7.3, 1.3 Hz), 7.05 (d, 2H, *J* = 8.4 Hz), 6.56 (s, 1H), 5.79 (d, 1H, *J* = 4.4 Hz), 4.97 (d, 1H, *J* = 4.4 Hz), 4.88 (d, 1H, *J* = 14.9 Hz), 4.02 (d, 1H, *J* = 14.9 Hz), 3.56 (s, 3H), 1.71 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 169.6, 164.1, 138.0, 133.3, 132.1, 130.7, 130.8, 127.1, 122.3, 122.1, 120.7, 119.9, 109.3, 102.9, 77.5, 54.0, 29.7, 20.0; IR ($CHCl_3$, cm^{-1}): ν 2929, 1741, 1226, 730; HRMS (ES): calcd for $C_{21}H_{19}BrN_2O_3$ [*M*]$^+$: 426.0579; found: 426.0560.

Acetoxy β-Lactam 23e. From 846 mg (3.95 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **23e** (740 mg, 60%) as a colorless solid; mp 112–113 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.64 (d, 1H, *J* = 7.9 Hz), 7.35 (d, 1H, *J* = 7.9 Hz), 7.27 (td, 1H, *J* = 7.4, 1.2 Hz), 7.15 (td, 1H, *J* = 7.4, 1.1 Hz), 6.55 (s, 1H), 5.87 (d, 1H, *J* = 4.4 Hz), 5.23 (d, 1H, *J* = 4.4 Hz), 3.73 (s, 3H), 3.43 (dd, 1H, *J* = 14.0, 8.5 Hz), 2.92 (dd, 1H, *J* = 14.0, 5.9 Hz), 1.93 (m, 1H), 1.93 (s, 3H), 0.98 (d, 3H, *J* = 6.7 Hz), 0.95 (d, 3H, *J* = 6.7 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 169.7, 164.7, 138.0, 131.1, 127.0, 122.0, 120.7, 119.8, 109.2, 102.8, 77.4, 55.4, 47.8, 29.8, 27.1, 20.3, 20.2, 20.0; IR ($CHCl_3$, cm^{-1}): ν 2923, 1742, 1211, 704; HRMS (ES): calcd for $C_{18}H_{22}N_2O_3$ [*M*]$^+$: 314.1630; found: 314.1641.

Acetoxy β-Lactam 23f. From 1.3 g (5.7 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave compound **23f** (592 mg, 45%) as a colorless solid; mp 138–139 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.55 (d, 1H, *J* = 7.9 Hz), 7.37 (m, 3H), 7.27 (m, 3H), 7.13 (m, 2H), 6.54 (s, 1H), 6.03 (d, 1H, *J* = 4.8 Hz), 5.63 (d, 1H, *J* = 4.8 Hz), 3.79 (s, 3H), 1.75 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 169.6, 161.5, 138.2, 136.5, 130.3, 129.2 (2C), 127.1, 124.9, 122.1, 120.8, 119.8, 117.5 (2C), 109.2, 103.7, 76.4, 55.3, 30.1, 20.0; IR ($CHCl_3$, cm^{-1}): ν 2923, 1744, 1215, 730, 699; HRMS (ES): calcd for $C_{20}H_{18}N_2O_3$ [*M*]$^+$: 334.1317; found: 334.1325.

Transesterification of Acetate Derivatives 23. General Procedure for the Preparation of Hydroxy-β-Lactams 24. Sodium methoxide (102 mg, 1.89 mmol) was added in portions at 0 ºC to a solution of the appropriate acetate derivative **23** (1.89 mmol) in methanol (18 mL). The reaction was stirred at 0 ºC until disappearance of the starting material (TLC) and then water was added (3 mL). The methanol was removed under reduced pressure, the aqueous residue was extracted with ethyl acetate and the organic layer was dried ($MgSO_4$). The solvent was removed under reduced pressure, to give analytically pure hydroxy-β-lactams **24**.

Hydroxy β-Lactam 24a. From 685 mg (2.0 mmol) of the acetoxy β-lactam **23a**, compound **24a** (479 mg, 80%) was obtained as a colorless solid; mp 129–130 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.64 (d, 1H, *J* = 7.8 Hz), 7.33 (m, 5H), 7.18 (m, 3H), 6.55 (s, 1H), 5.07 (br s, 1H), 5.00 (d, 1H, *J* = 14.8 Hz), 4.92 (d, 1H, *J* = 4.8 Hz), 4.12 (d, 1H, *J* = 14.8 Hz), 3.62 (s, 3H), 2.47 (br s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 168.0, 134.7 (2C), 132.9, 129.0 (2C), 128.6 (2C), 128.1, 127.2, 122.4, 120.7, 120.2, 109.2, 101.7, 78.5, 55.5, 44.2, 30.0; IR ($CHCl_3$, cm^{-1}): ν 3102, 2925, 1670, 1612, 750, 701; HRMS (ES): calcd for $C_{19}H_{18}N_2O_2$ [*M*]$^+$: 306.1368; found: 306.1364.

Hydroxy β-Lactam 24b. From 800 mg (2.11 mmol) of the acetoxy β-lactam **23b**, compound **24b** (685 mg, 96%) was obtained as a colorless solid; mp 139–140 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.63 (d, 1H, *J* = 7.8 Hz), 7.29 (m, 2H), 7.17 (m, 1H), 7.12 (d,

2H, *J* = 8.3 Hz), 6.85 (d, 2H, *J* = 8.2 Hz), 6.55 (s, 1H), 5.05 (d, 1H, *J* = 4.2 Hz), 4.92 (m, 1H), 4.88 (m, 1H), 4.06 (d, 1H, *J* = 14.7 Hz), 3.80 (s, 1H), 3.62 (s, 3H), 2.78 (br s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 168.1, 159.4, 138.5, 133.0, 129.9 (2C), 127.2, 126.7, 122.0, 120.7, 120.0, 114.3 (2C), 109.1, 101.7, 78.3, 55.3 (2C), 43.6, 30.0; IR ($CHCl_3$, cm^{-1}): ν 3100, 2924, 1650, 1610, 730; HRMS (ES): calcd for $C_{20}H_{20}N_2O_3$ [*M*]$^+$: 336.1474; found: 336.1460.

Hydroxy β-Lactam 24c. From 940 mg (2.57 mmol) of the acetoxy β-lactam **23c**, compound **24c** (790 mg, 95%) was obtained as a colorless solid; mp 138–139 ºC; ^{1}H-NMR (300 MHz, DMSO, 25 ºC) δ: 7.43 (d, 1H, *J* = 8.2 Hz), 7.35 (d, 2H, *J* = 9.0 Hz), 7.12 (t, 1H, *J* = 7.3 Hz), 6.98 (t, 1H, *J* = 7.0 Hz), 6.92 (d, 2H, *J* = 8.9 Hz), 6.13 (s, 1H), 5.68 (d, 1H, *J* = 4.9 Hz), 5.30 (m, 1H), 3.75 (s, 1H), 3.71 (s, 3H); ^{13}C-NMR (75 MHz, DMSO, 25 ºC) δ: 165.9, 155.7, 137.7, 134.7, 130.7, 126.9, 120.9, 119.8, 119.0, 118.4 (2C), 114.4 (2C), 109.3, 100.9, 77.1, 56.4, 55.2, 30.0; IR ($CHCl_3$, cm^{-1}): ν 3101, 2924, 1667, 1615, 743; HRMS (ES): calcd for $C_{19}H_{18}N_2O_3$ [*M*]$^+$: 322.1317; found: 322.1326.

Hydroxy β-Lactam 24d. From 1.32 g (3.09 mmol) of the acetoxy β-lactam **23d**, compound **24d** (1.19 g, 99%) was obtained as a colorless solid; mp 133–134 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.63 (d, 1H, *J* = 7.8 Hz), 7.46 (d, 2H, *J* = 8.4 Hz), 7.33 (d, 1H, *J* = 7.9 Hz), 7.27 (td, 1H, *J* = 7.6, 1.2 Hz), 7.16 (td, 1H, *J* = 7.3, 1.3 Hz), 7.08 (d, 2H, *J* = 8.4 Hz), 6.52 (s, 1H), 5.06 (br s, 1H), 4.90 (d, 1H, *J* = 14.7 Hz), 4.89 (d, 1H, *J* = 5.0 Hz), 4.08 (d, 1H, *J* = 14.9 Hz), 3.62 (s, 3H), 3.00 (br s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 166.3, 138.5, 133.6, 132.6, 132.1 (2C), 130.2 (2C), 127.1, 122.3, 122.2, 120.7, 120.1, 109.2, 101.7, 78.4, 55.6, 43.6, 30.0; IR ($CHCl_3$, cm^{-1}): ν 3100, 2930, 1669, 1617, 723; HRMS (ES): calcd for $C_{19}H_{17}BrN_2O_2$ [*M*]$^+$: 384.0473; found: 384.0487.

Hydroxy β-Lactam 24e. From 678 mg (2.16 mmol) of the acetoxy β-lactam **23e**, compound **24e** (588 mg, 94%) was obtained as a colorless solid; mp 125–126 ºC; ^{1}H-NMR (300 MHz, DMSO, 25 ºC) δ: 7.50 (d, 1H, *J* = 7.7 Hz), 7.42 (d, 1H, *J* = 8.1 Hz), 7.12 (td, 1H, *J* = 7.6, 1.2 Hz), 7.01 (td, 1H, *J* = 7.4, 0.9 Hz), 6.34 (s, 1H), 6.09 (m, 1H), 5.15 (m, 1H), 3.68 (s, 3H), 3.27 (dd, 1H, *J* = 13.8, 8.6 Hz), 2.90 (dd, 1H, *J* = 13.8, 5.7 Hz), 1.86 (m, 1H), 0.88 (d, 3H, *J* = 6.7 Hz), 0.87 (d, 3H, *J* = 6.7 Hz); ^{13}C-NMR (75 MHz, DMSO, 25 ºC) δ: 168.9, 137.7, 135.8, 127.1, 120.8, 119.8, 118.9, 109.3, 100.3, 77.8, 56.7, 47.3, 29.8, 26.7, 20.2, 20.1; IR ($CHCl_3$, cm^{-1}): ν 3099, 2925, 1672, 1610, 690; HRMS (ES): calcd for $C_{16}H_{20}N_2O_2$ [*M*]$^+$: 272.1525; found: 272.1528.

Hydroxy β-Lactam 24f. From 595 mg (1.78 mmol) of the acetoxy β-lactam **23f**, compound **24f** (446 mg, 86%) was obtained as a colorless solid; mp 132–133 ºC; ^{1}H-NMR (300 MHz, DMSO, 25 ºC) δ: 7.42 (m, 3H), 7.34 (m, 3H), 7.11 (m, 2H), 6.98 (t, 1H, *J* = 7.5 Hz), 6.43 (d, 1H, *J* = 7.6 Hz), 6.13 (s, 1H), 5.73 (d, 1H, *J* = 5.1 Hz), 5.33 (dd, 1H, *J* = 7.6, 5.1 Hz), 3.77 (s, 3H); ^{13}C-NMR (75 MHz, DMSO, 25 ºC) δ: 166.7, 137.8, 137.3, 134.6, 129.2 (2C), 127.0, 123.9, 120.9, 119.9, 119.0, 117.2 (2C), 109.3, 100.8, 77.1, 56.3, 30.0; IR ($CHCl_3$, cm^{-1}): ν 3102, 2923, 1670, 1613, 752, 698; HRMS (ES): calcd for $C_{18}H_{16}N_2O_2$ [*M*]$^+$: 292.1212; found: 292.1221.

Base-promoted reaction between propargyl bromide and hydroxy-β-lactams 24. General procedure for the synthesis of propargylic ethers 25a–f. Tetrabutyl ammonium iodide (31.9 mg, 0.086 mmol), 50% aqueous sodium hydroxide (100 mL), and propargyl bromide (13.82 mmol), were sequentially added at room temperature to a solution of the appropriate hydroxy-β-lactam **24** (8.64 mmol) in dichloromethane (100 mL). The reaction was stirred for 20 h and then water was added (50 mL), before being partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (3 x 50 mL), the combined organic extracts were washed with brine, dried

($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/hexanes mixtures as eluent gave analytically pure compounds **25**.

Alkynyl β-Lactam 25a. From 470 mg (1.55 mmol) of hydroxy-β-lactam **24a**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **25a** (421 mg, 79%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.63 (d, 1H, *J* = 7.9 Hz), 7.31 (m, 4H), 7.26 (m, 1H), 7.17 (m, 3H), 6.59 (s, 1H), 5.19 (d, 1H, *J* = 4.5 Hz), 4.95 (d, 1H, *J* = 14.6 Hz), 4.88 (d, 1H, *J* = 4.7 Hz), 4.25 (dd, 1H, *J* = 16.1, 2.5 Hz), 4.05 (d, 1H, *J* = 15.0 Hz), 4.00 (dd, 1H, *J* = 16.1, 2.3 Hz), 3.62 (s, 3H), 2.40 (t, 1H, *J* = 2.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 166.3, 138.4, 134.6, 132.3, 128.9 (2C), 128.6 (2C), 128.0, 127.4, 122.0, 120.7, 119.8, 109.1, 103.2, 82.4, 78.2, 75.9, 57.8, 54.4, 44.3, 30.3; IR ($CHCl_3$, cm^{-1}): ν 2926, 1753, 1615, 1395, 752, 701; HRMS (ES): calcd for $C_{22}H_{20}N_2O_2$ [*M*]$^+$: 344.1525; found: 344.1515.

Alkynyl β-Lactam 25b. From 403 mg (1.20 mmol) of hydroxy-β-lactam **24b**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **25b** (403 mg, 90%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.63 (d, 1H, *J* = 7.9 Hz), 7.28 (m, 2H), 7.14 (t, 1H, *J* = 7.9 Hz), 7.09 (d, 2H, *J* = 8.6 Hz), 6.83 (d, 2H, *J* = 8.6 Hz), 6.58 (s, 1H), 5.17 (d, 1H, *J* = 4.7 Hz), 4.87 (m, 1H), 4.85 (m, 1H), 4.24 (dd, 1H, *J* = 16.1, 2.3 Hz), 4.00 (d, 1H, *J* = 14.8 Hz), 3.98 (d, 1H, *J* = 16.1 Hz), 3.80 (s, 3H), 3.62 (s, 3H), 2.39 (t, 1H, *J* = 2.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 166.2, 159.4, 138.3, 132.4, 130.0 (2C), 127.4, 126.6, 121.9, 120.7, 119.7, 114.2 (2C), 109.1, 103.2, 82.3, 78.2, 75.8, 57.7, 55.3, 54.2, 43.7, 30.3; IR ($CHCl_3$, cm^{-1}): ν 2924, 1760, 1624, 1245, 734; HRMS (ES): calcd for $C_{23}H_{22}N_2O_3$ [*M*]$^+$: 374.1630; found: 374.1641.

Alkynyl β-Lactam 25c. From 745 mg (2.31 mmol) of hydroxy-β-lactam **24c**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **25c** (367 mg, 44%) as a colorless solid; mp 154–155 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.57 (d, 1H, *J* = 7.9 Hz), 7.36 (d, 2H, *J* = 9.0 Hz), 7.34 (m, 1H), 7.25 (t, 1H, *J* = 7.5 Hz), 7.12 (t, 1H, *J* = 7.4 Hz), 6.81 (d, 2H, *J* = 9.1 Hz), 6.56 (s, 1H), 5.51 (d, 1H, *J* = 5.0 Hz), 5.35 (d, 1H, *J* = 5.0 Hz), 4.31 (dd, 1H, *J* = 16.1, 2.4 Hz), 4.08 (dd, 1H, *J* = 16.1, 2.4 Hz), 3.79 (s, 3H), 3.76 (s, 3H), 2.47 (t, 1H, *J* = 2.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 163.3, 156.5, 138.6, 131.8, 130.6, 127.2, 122.0, 120.7, 119.7, 118.7 (2C), 114.4 (2C), 109.1, 103.9, 81.4, 78.1, 76.1, 57.9, 56.1, 55.5, 30.7; IR ($CHCl_3$, cm^{-1}): ν 2920, 1757, 1614, 1360, 746; HRMS (ES): calcd for $C_{22}H_{20}N_2O_3$ [*M*]$^+$: 360.1474; found: 360.1458.

Alkynyl β-Lactam 25d. From 1.3 g (3.37 mmol) of hydroxy-β-lactam **24d**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **25d** (970 mg, 68%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.63 (d, 1H, *J* = 7.8 Hz), 7.45 (d, 2H, *J* = 8.4 Hz), 7.33 (d, 1H, *J* = 7.8 Hz), 7.26 (td, 1H, *J* = 7.0, 1.2 Hz), 7.15 (td, 1H, *J* = 7.3, 1.2 Hz), 7.06 (d, 2H, *J* = 8.4 Hz), 6.56 (s, 1H), 5.20 (d, 1H, *J* = 4.7 Hz), 4.87 (d, 1H, *J* = 14.8 Hz), 4.87 (d, 1H, *J* = 4.7 Hz), 4.25 (dd, 1H, *J* = 16.1, 2.4 Hz), 4.02 (d, 1H, *J* = 14.9 Hz), 4.00 (dd, 1H, *J* = 16.1, 2.4 Hz), 3.64 (s, 3H), 2.41 (t, 1H, *J* = 2.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 166.3, 138.3, 133.6 (2C), 132.0 (2C), 130.3 (2C), 127.2, 122.1, 122.0, 120.7, 119.8, 109.1, 103.2, 82.4, 78.0, 76.0, 57.8, 54.5, 43.6, 30.3; IR ($CHCl_3$, cm^{-1}): ν 2920, 1753, 1640, 1390, 735; HRMS (ES): calcd for $C_{22}H_{19}BrN_2O_2$ [*M*]$^+$: 422.0630; found: 422.0641.

Alkynyl β-Lactam 25e. From 530 mg (1.95 mmol) of hydroxy-β-lactam **24e**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **25e** (552 mg, 91%) as a colorless solid; mp 98–99 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.61 (d, 1H, *J* = 7.8 Hz), 7.35 (d, 1H, *J* = 8.2 Hz), 7.26 (td, 1H, *J* = 7.4, 1.2 Hz), 7.17 (td, 1H, *J* = 7.4, 1.1 Hz), 6.55 (s, 1H), 5.26 (d, 1H, *J* = 4.6 Hz), 5.11 (d, 1H, *J* =

4.6 Hz), 4.25 (dd, 1H, *J* = 16.1, 2.4 Hz), 4.00 (dd, 1H, *J* = 16.1, 2.4 Hz), 3.77 (s, 3H), 3.42 (dd, 1H, *J* = 13.9, 8.5 Hz), 2.87 (dd, 1H, *J* = 13.9, 5.8 Hz), 2.42 (t, 1H, *J* = 2.4 Hz), 1.90 (m, 1H), 0.94 (d, 3H, *J* = 6.5 Hz), 0.92 (d, 3H, *J* = 6.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 167.0, 138.4, 132.5, 127.2, 122.0, 120.7, 119.8, 109.1, 103.3, 82.1, 78.2, 75.8, 57.7, 56.0, 47.8, 30.5, 27.1, 20.3, 20.2; IR ($CHCl_3$, cm^{-1}): ν 2930, 1763, 1640, 1390, 690; HRMS (ES): calcd for $C_{19}H_{22}N_2O_2$ [*M*]$^+$: 310.1681; found: 310.1681.

Alkynyl β-Lactam 25f. From 424 mg (1.45 mmol) of hydroxy-β-lactam **24f**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **25f** (172 mg, 36%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.58 (d, 1H, *J* = 7.9 Hz), 7.43 (d, 2H, *J* = 7.6 Hz), 7.30 (m, 4H), 7.11 (t, 2H, *J* = 7.3 Hz), 6.57 (s, 1H), 5.55 (d, 1H, *J* = 5.1 Hz), 5.37 (d, 1H, *J* = 5.1 Hz), 4.32 (dd, 1H, *J* = 16.1, 2.3 Hz), 4.08 (dd, 1H, *J* = 16.1, 2.4 Hz), 3.76 (s, 3H), 2.48 (t, 1H, *J* = 2.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 163.9, 138.5, 137.0, 131.6, 129.2 (2C), 127.2, 124.7, 122.0, 120.7, 119.7, 117.4 (2C), 109.1, 103.8, 81.3, 78.0, 76.2, 57.9, 56.0, 30.7; IR ($CHCl_3$, cm^{-1}): ν 2934, 1750, 1614, 1425, 750, 703; HRMS (ES): calcd for $C_{21}H_{18}N_2O_2$ [*M*]$^+$: 330.1368; found: 330.1363.

Staudinger Reaction. General Procedure for the Preparation of Alkynyl β-Lactam-Tethered Indoles 26a–f. To a solution of the corresponding imine (10.4 mmol) in dichloromethane (35 mL) and triethylamine (4.2 mL, 30 mmol) was slowly added methoxyacetyl chloride (13 mmol) dissolved in dichloromethane (35 mL) at room temperature under an argon atmosphere. Stirring was continued for 2 h at 80ºC. The reaction was allowed to warm to room temperature and then, 15 mL of $NaHCO_3$ (aq. sat.) were added before being partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (3 x 50 mL), the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/hexanes mixture gave analytically pure compounds **26**.

Alkynyl β-Lactam 26a. From 632 mg (3.22 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **26a** (641 mg, 74%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.62 (dd, 1H, *J* = 7.8, 0.9 Hz), 7.36 (dd, 1H, *J* = 8.3, 0.8 Hz), 7.26 (td, 1H, *J* = 8.3, 1.2 Hz), 7.14 (td, 1H, *J* = 7.4, 1.1 Hz), 6.58 (s, 1H), 5.19 (d, 1H, *J* = 4.7 Hz), 4.87 (d, 1H, *J* = 4.7 Hz), 4.47 (dd, 1H, *J* = 17.7, 2.6 Hz), 3.82 (dd, 1H, *J* = 17.6, 2.5 Hz), 3.82 (s, 3H), 3.31 (s, 3H), 2.25 (t, 1H, *J* = 2.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 166.1, 138.4, 132.3, 127.3, 122.0, 120.7, 119.8, 109.1, 103.0, 86.1, 75.9, 73.0, 58.5, 54.9, 30.4, 29.7; IR ($CHCl_3$, cm^{-1}): ν 2920, 1750, 1618, 1246, 1243; HRMS (ES): calcd for $C_{16}H_{16}N_2O_2$ [*M*]$^+$: 268.1212; found: 268.1224.

Alkynyl β-Lactam 26b. From 678 mg (2.94 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **26b** (689 mg, 77%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.56 (d, 1H, *J* = 1.5 Hz), 7.26 (d, 1H, *J* = 8.9 Hz), 7.19 (dd, 1H, *J* = 8.8, 2.0 Hz), 6.51 (s, 1H), 5.15 (d, 1H, *J* = 4.8 Hz), 4.87 (d, 1H, *J* = 4.7 Hz), 4.45 (dd, 1H, *J* = 17.7, 2.5 Hz), 3.82 (dd, 1H, *J* = 17.7, 2.5 Hz), 3.77 (s, 3H), 3.31 (s, 3H), 2.25 (t, 1H, *J* = 2.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 166.0, 136.7, 133.9, 128.2, 125.5, 122.3, 120.0, 110.1, 102.5, 86.1, 75.8, 73.2, 58.6, 54.8, 30.6, 29.8; IR ($CHCl_3$, cm^{-1}): ν 2926, 1751, 1620, 1256, 1237; HRMS (ES): calcd for $C_{16}H_{15}ClN_2O_2$ [*M*]$^+$: 302.0822; found: 302.0825.

Alkynyl β-Lactam 26c. From 324 mg (1.43 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **26c** (271 mg, 71%) as a colorless solid; mp 160–161 ºC; ^{1}H-NMR (300 MHz,

$CDCl_3$, 25 °C) δ: 7.24 (d, 1H, *J* = 8.9 Hz), 7.07 (d, 1H, *J* = 2.5 Hz), 6.91 (dd, 1H, *J* = 8.9, 2.5 Hz), 6.49 (s, 1H), 5.15 (d, 1H, *J* = 4.6 Hz), 4.86 (d, 1H, *J* = 4.6 Hz), 4.45 (dd, 1H, *J* = 17.7, 2.5 Hz), 3.86 (s, 3H), 3.80 (dd, 1H, *J* = 17.7, 2.5 Hz), 3.76 (s, 3H), 3.30 (s, 3H), 2.25 (t, 1H, *J* = 2.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ: 166.1, 154.3, 133.7, 132.7, 127.6, 112.4, 109.8, 102.5, 102.3, 86.1, 75.9, 73.0, 58.5, 55.9, 54.8, 30.5, 29.7; IR ($CHCl_3$, cm^{-1}): ν 2932, 1756, 1635, 1260, 1248; HRMS (ES): calcd for $C_{17}H_{18}N_2O_3$ $[M]^+$: 298.1317; found: 298.1317.

Alkynyl β-Lactam 26d. From 884 mg (4.17 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **26d** (696 mg, 59%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.81 (d, 1H, *J* = 7.8 Hz), 7.35 (d, 1H, *J* = 8.2 Hz), 7.25 (td, 1H, *J* = 7.6, 1.2 Hz), 7.13 (td, 1H, *J* = 7.4, 1.1 Hz), 6.56 (s, 1H), 5.24 (d, 1H, *J* = 4.6 Hz), 4.89 (d, 1H, *J* = 4.6 Hz), 3.80 (m, 1H), 3.78 (s, 3H), 3.29 (s, 3H), 3.23 (m, 1H), 2.47 (m, 2H), 2.01 (t, 1H, *J* = 2.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ: 167.0, 138.4, 132.7, 127.3, 122.0, 120.7, 119.8, 109.1, 103.1, 86.0, 80.7, 70.5, 58.5, 56.1, 38.8, 30.5, 17.8; IR ($CHCl_3$, cm^{-1}): ν 2920, 1747, 1630, 1259, 1230; HRMS (ES): calcd for $C_{17}H_{18}N_2O_2$ $[M]^+$: 282.1368; found: 282.1376.

Alkynyl β-Lactam 26e. From 700 mg (2.86 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **26e** (589 mg, 65%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.54 (d, 1H, *J* = 1.9 Hz), 7.24 (d, 1H, *J* = 8.8 Hz), 7.17 (dd, 1H, *J* = 8.8, 2.0 Hz), 6.48 (s, 1H), 5.21 (d, 1H, *J* = 4.6 Hz), 4.87 (d, 1H, *J* = 4.6 Hz), 3.77 (m, 1H), 3.75 (s, 3H), 3.28 (s, 3H), 3.22 (m, 1H), 2.48 (m, 2H), 2.01 (t, 1H, *J* = 2.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ: 166.8, 136.7, 134.3, 128.1, 125.4, 122.1, 119.9, 110.1, 102.4, 85.9, 80.6, 70.5, 58.5, 55.9, 38.9, 30.6, 17.8; IR ($CHCl_3$, cm^{-1}): ν 2932, 1754, 1610, 1390, 1215; HRMS (ES): calcd for $C_{17}H_{17}ClN_2O_2$ $[M]^+$: 316.0979; found: 316.0969.

Alkynyl β-Lactam 26f. From 406 mg (1.69 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **26f** (247 mg, 47%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.23 (d, 1H, *J* = 8.9 Hz), 7.06 (d, 1H, *J* = 2.4 Hz), 6.91 (dd, 1H, *J* = 8.9, 2.5 Hz), 6.47 (s, 1H), 5.19 (d, 1H, *J* = 4.6 Hz), 4.87 (d, 1H, *J* = 4.6 Hz), 3.85 (s, 3H), 3.79 (m, 1H), 3.74 (s, 3H), 3.28 (s, 3H), 3.25 (m, 1H), 2.48 (m, 2H), 2.01 (t, 1H, *J* = 2.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ: 167.0, 154.2, 133.8, 133.1, 127.5, 122.4, 109.8, 102.6, 102.2, 86.0, 80.7, 70.5, 58.5, 56.0, 55.8, 38.8, 30.9, 17.8; IR ($CHCl_3$, cm^{-1}): ν 2926, 1758, 1623, 1298, 1234; HRMS (ES): calcd for $C_{18}H_{20}N_2O_3$ $[M]^+$: 312.1474; found: 312.1470.

Cu-Catalyzed Reaction of β-Lactam-Tethered Alkynyl Indoles 25 and 26. General Procedure for the Preparation of β-Lactam-Tethered Allenyl Indoles 27a–f and 28a–f. A well stirred solution of $(CH_2O)_n$ (0.5 mmol), CuI (0.1 mmol), the appropriate alkyne **25** or **26** (0.2 mmol), and *N*,*N*-diisopropylethylamine (Hüning's base) (0.36 mmol) in dioxane (1 mL) was refluxed under argon atmosphere. When the reaction was complete as monitored by TLC, it was cooled to RT. Water (5 mL) was added before being extracted with ethyl acetate (3 x 15 mL). The organic phase was washed with water (2 x 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds **27** or **28**. Spectroscopic and analytical data for previously allenes **27** or **28** follow.

Allenyl β-Lactam 27a. From 406 mg (1.20 mmol) of alkynyl-β-lactam **25a**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **27a** (266 mg, 63%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.62 (d, 1H, *J* = 7.8 Hz), 7.28 (m, 5H), 7.15 (m, 3H), 6.59 (s, 1H), 4.98 (d, 1H, *J* = 4.5 Hz), 4.92

(d, 1H, *J* = 14.9 Hz), 4.91 (m, 1H), 4.83 (d, 1H, *J* = 4.4 Hz), 4.64 (m, 2H), 4.01 (d, 1H, *J* = 14.7 Hz), 3.96 (t, 1H, *J* = 2.3 Hz), 3.94 (t, 1H, *J* = 2.3 Hz), 3.62 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 209.6, 166.7, 138.4, 134.7, 132.4, 128.9 (2C), 128.7 (2C), 128.0, 127.4, 121.9, 120.7, 119.7, 109.1, 103.6, 86.7, 83.5, 75.8, 68.7, 55.0, 44.2, 30.4; IR ($CHCl_3$, cm^{-1}): ν 2953, 1756, 1616, 1397, 751, 701; HRMS (ES): calcd for $C_{23}H_{22}N_2O_2$ [*M*]$^+$: 358.1681; found: 358.1693.

Allenyl β-Lactam 27b. From 434 mg (1.16 mmol) of alkynyl-β-lactam **25b**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound **27b** (353 mg, 78%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.62 (d, 1H, *J* = 7.7 Hz), 7.32 (d, 1H, *J* = 8.0 Hz), 7.25 (td, 1H, *J* = 8.1, 1.2 Hz), 7.14 (td, 1H, *J* = 7.9, 1,2 Hz), 7.08 (d, 2H, *J* = 8.6 Hz), 6.82 (d, 2H, *J* = 8.6 Hz), 6.58 (s, 1H), 4.96 (d, 1H, *J* = 4.5 Hz), 4.92 (t, 1H, *J* = 6.9 Hz), 4.85 (d, 1H, *J* = 14.5 Hz), 4.80 (d, 1H, *J* = 4.5 Hz), 4.63 (m, 2H), 3.96 (d, 1H, *J* = 14.9 Hz), 3.94 (m, 2H), 3.79 (s, 3H), 3.62 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 209.6, 166.5, 159.3, 138.4, 132.6, 130.0 (2C), 127.4, 126.7, 121.9, 120.7, 119.7, 114.2 (2C), 109.1, 103.6, 86.7, 83.5, 75.7, 68.7, 55.3, 54.8, 43.7, 30.4; IR ($CHCl_3$, cm^{-1}): ν 2950, 1752, 1615, 1398, 734; HRMS (ES): calcd for $C_{24}H_{24}N_2O_3$ [*M*]$^+$: 388.1787; found: 388.1784.

Allenyl β-Lactam 27c. From 262 mg (0.73 mmol) of alkynyl-β-lactam **25c**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **27c** (165 mg, 60%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.49 (d, 1H, *J* = 7.9 Hz), 7.27 (d, 2H, *J* = 9.0 Hz), 7.25 (d, 1H, *J* = 8.2 Hz), 7.16 (td, 1H, *J* = 8.3, 1,2 Hz), 7.03 (td, 1H, *J* = 7.9, 1.0 Hz), 6.71 (d, 2H, *J* = 9.1 Hz), 6.49 (s, 1H), 5.38 (d, 1H, *J* = 4.8 Hz), 5.06 (d, 1H, *J* = 4.8 Hz), 4.90 (q, 1H, *J* = 6.9 Hz), 4.57 (m, 2H), 3.94 (dd, 2H, *J* = 6.8, 1.2 Hz), 3.70 (s, 3H), 3.67 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 209.7, 163.7, 156.5, 138.7, 132.0, 130.7, 127.3, 122.0, 120.7, 119.7, 118.7, 114.4 (2C), 109.1, 104.2, 86.7, 82.7, 75.8, 68.8, 56.8, 55.4, 30.9; IR ($CHCl_3$, cm^{-1}): ν 2945, 1759, 1618, 1387, 735; HRMS (ES): calcd for $C_{23}H_{22}N_2O_3$ [*M*]$^+$: 374.1630; found: 374.1616.

Allenyl β-Lactam 27d. From 489 mg (1.55 mmol) of alkynyl-β-lactam **25d**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **27d** (339 mg, 50%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.63 (d, 1H, *J* = 7.7 Hz), 7.44 (d, 2H, *J* = 8.3 Hz), 7.33 (d, 1H, *J* = 8.2 Hz), 7.26 (td, 1H, *J* = 6.9, 1.2 Hz), 7.14 (t, 1H, *J* = 7.9 Hz), 7.05 (d, 2H, *J* = 8.5 Hz), 6.57 (s, 1H), 4.99 (d, 1H, *J* = 4.5 Hz), 4.92 (qu, 1H, *J* = 7.0 Hz), 4.85 (d, 1H, *J* = 12.7 Hz), 4.82 (d, 1H, *J* = 4.4 Hz), 4.65 (m, 2H), 3.99 (d, 1H, *J* = 12.2 Hz), 3.96 (m, 2H), 3.64 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 209.6, 166.6, 138.4, 133.7, 132.1, 132.0 (2C), 130.3 (2C), 127.3, 122.1, 122.0, 120.7, 119.8, 109.1, 103.6, 86.6, 83.5, 75.8, 68.8, 55.0, 43.6, 30.5; IR ($CHCl_3$, cm^{-1}): ν 2952, 1758, 1620, 1297, 754; HRMS (ES): calcd for $C_{23}H_{21}BrN_2O_2$ [*M*]$^+$: 436.0786; found: 436.0799.

Allenyl β-Lactam 27e. From 524 mg (1.69 mmol) of alkynyl-β-lactam **25e**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **27e** (443 mg, 81%) as a colorless solid; mp 98–99 ^{o}C; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.61 (d, 1H, *J* = 7.7 Hz), 7.35 (d, 1H, *J* = 8.2 Hz), 7.25 (td, 1H, *J* = 7.4, 1.2 Hz), 7.13 (td, 1H, *J* = 7.3, 1.2 Hz), 6.56 (s, 1H), 5.07 (m, 1H), 5.05 (m, 1H), 4.94 (q, 1H, *J* = 6.7 Hz), 4.65 (m, 2H), 3.96 (m, 2H), 3.78 (s, 3H), 3.89 (dd, 1H, *J* = 13.9, 8.5 Hz), 2.83 (dd, 1H, *J* = 13.9, 5.9 Hz), 1.89 (m, 1H), 0.93 (d, 3H, *J* = 6.6 Hz), 0.91 (d, 3H, *J* = 6.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 209.5, 167.3, 138.4, 132.6, 127.3, 121.9, 120.6, 119.7, 109.1, 103.7, 86.7, 83.3, 75.7, 68.7, 56.6, 47.8, 30.6, 27.1, 20. 4, 20.3; IR ($CHCl_3$, cm^{-1}): ν 2953, 1759, 1614, 1395, 741; HRMS (ES): calcd for $C_{20}H_{24}N_2O_2$ [*M*]$^+$: 324.1838; found: 324.1845.

Allenyl β-Lactam 27f. From 68 mg (0.21 mmol) of alkynyl-β-lactam **25f**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **27f** (30 mg, 42%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.59 (d, 1H, *J* = 7.8 Hz), 7.43 (d, 2H, *J* = 8.5 Hz), 7.28 (m, 4H), 7.14 (d, 1H, *J* = 7.9 Hz), 7.10 (t, 1H, *J* = 7.4 Hz), 6.60 (s, 1H), 5.52 (d, 1H, *J* = 4.9 Hz), 5.17 (d, 1H, *J* = 5.0 Hz), 5.00 (q, 1H, *J* = 6.9 Hz), 4.67 (m, 2H), 4.04 (dt, 2H, *J* = 7.2, 2.2 Hz), 3.80 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 209.7, 164.3, 138.7, 137.1, 131.9, 129.2 (2C), 127.2, 124.6, 122.0, 120.7), 119.7, 117.3 (2C), 109.1, 104.1, 86.6, 82.6, 75.8, 68.9, 56.6, 30.9; IR ($CHCl_3$, cm^{-1}): ν 2955, 1755, 1619, 1395, 752, 700; HRMS (ES): calcd for $C_{22}H_{20}N_2O_2$ [*M*]$^+$: 344.1525; found: 344.1519.

Allenyl β-Lactam 28a. From 292 mg (1.1 mmol) of alkynyl-β-lactam **26a**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **28a** (236 mg, 77%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.61 (d, 1H, *J* = 7.9 Hz), 7.35 (d, 1H, *J* = 8.0 Hz), 7.25 (td, 1H, *J* = 8.2, 1.0 Hz), 7.13 (td, 1H, *J* = 7.5, 0.9 Hz), 6.57 (s, 1H), 5.12 (d, 1H, *J* = 4.5 Hz), 5.11 (m, 1H), 4.85 (d, 1H, *J* = 4.7 Hz), 4.80 (m, 2H), 4.27 (m, 1H), 3.78 (s, 3H), 3.60 (m, 1H), 3.30 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 209.2, 166.7, 138.4, 132.8, 127.3, 121.9, 120.7, 119.7, 109.0, 103.1, 85.9, 85.1, 77.4, 58.5, 55.3, 38.6, 30.4; IR ($CHCl_3$, cm^{-1}): ν 2954, 1760, 1616, 1390, 1240; HRMS (ES): calcd for $C_{17}H_{18}N_2O_2$ [*M*]$^+$: 282.1368; found: 282.1379.

Allenyl β-Lactam 28b. From 320 mg (1.06 mmol) of alkynyl-β-lactam **26b**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **28b** (201 mg, 60%) as a colorless solid; mp 105–106 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.56 (d, 1H, *J* = 1.9 Hz), 7.25 (d, 1H, *J* = 8.8 Hz), 7.18 (dd, 1H, *J* = 8.7, 1.9 Hz), 6.50 (s, 1H), 5.10 (m, 1H), 5.09 (d, 1H, *J* = 5.0 Hz), 4.85 (d, 1H, *J* = 4.7 Hz), 4.80 (m, 2H), 4.26 (m, 1H), 3.75 (s, 3H), 3.60 (m, 1H), 3.30 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 209.2, 166.6, 136.7, 134.3, 128.2, 125.4, 122.1, 120.0, 110.1, 102.5, 85.8, 85.0, 77.9, 58.5, 55.1, 38.7, 30.7; IR ($CHCl_3$, cm^{-1}): ν 2950, 1753, 1624, 1379, 1251; HRMS (ES): calcd for $C_{17}H_{17}ClN_2O_2$ [*M*]$^+$: 316.0979; found: 316.0977.

Allenyl β-Lactam 28c. From 170 mg (0.57 mmol) of alkynyl-β-lactam **26c**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **28c** (84 mg, 47%) as a colorless solid; mp 111–112 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.23 (d, 1H, *J* = 8.9 Hz), 7.06 (d, 1H, *J* = 2.4 Hz), 6.91 (dd, 1H, *J* = 8.9, 2.5 Hz), 6.48 (s, 1H), 5.10 (m, 1H), 5.09 (d, 1H, *J* = 4.6 Hz), 4.84 (d, 1H, *J* = 4.6 Hz), 4.80 (m, 2H), 4.26 (m, 1H), 3.85 (s, 3H), 3.74 (s, 3H), 3.59 (m, 1H), 3.29 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 209.2, 166.7, 154.3, 133.8, 133.1, 127.6, 112.3, 109.8, 102.7, 102.3, 85.9, 85.1, 77.4, 58.5, 55.9, 55.2, 38.5, 30.6; IR ($CHCl_3$, cm^{-1}): ν 2950, 1755, 1623, 1387, 1236; HRMS (ES): calcd for $C_{18}H_{20}N_2O_3$ [*M*]$^+$: 312.1474; found: 312.1474.

Allenyl β-Lactam 28d. From 215 mg (0.76 mmol) of alkynyl-β-lactam **26d**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **28d** (104 mg, 46%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.51 (d, 1H, *J* = 7.8 Hz), 7.25 (d, 1H, *J* = 8.2 Hz), 7.15 (td, 1H, *J* = 7.6, 1.2 Hz), 7.03 (td, 1H, *J* = 7.4, 1.1 Hz), 6.46 (s, 1H), 4.98 (d, 1H, *J* = 4.5 Hz), 4.97 (m, 1H), 4.70 (d, 1H, *J* = 4.7 Hz), 4.62 (m, 2H), 3.67 (s, 3H), 3.62 (m, 1H), 3.17 (s, 3H), 3.06 (m, 1H), 2.15 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 208.7, 166.8, 138.3, 132.8, 127.2, 121.8, 120.5, 119.6, 109.0, 103.0, 86.5, 85.7, 75.7, 58.3, 55.6, 39.5, 30.4, 26.1; IR ($CHCl_3$, cm^{-1}): ν 2960, 1757, 1616, 1387, 1234; HRMS (ES): calcd for $C_{18}H_{20}N_2O_2$ [*M*]$^+$: 296.1525; found: 296.1525.

Allenyl β-Lactam 28e. From 166 mg (0.52 mmol) of alkynyl-β-lactam **26e**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave

compound **28e** (95 mg, 55%) as a colorless solid; mp 98–99 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.56 (d, 1H, *J* = 1.9 Hz), 7.25 (d, 1H, *J* = 8.8 Hz), 7.18 (td, 1H, *J* = 8.7, 2.0 Hz), 6.49 (s, 1H), 5.05 (q, 1H, *J* = 6.7 Hz), 5.04 (d, 1H, *J* = 4.5 Hz), 4.81 (d, 1H, *J* = 4.6 Hz), 4.72 (m, 2H), 3.75 (s, 3H), 3.69 (m, 1H), 3.29 (s, 3H), 3.16 (m, 1H), 2.25 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 208.8, 166.9, 136.8, 134.4, 128.2, 125.5, 122.2, 120.0, 110.1, 102.6, 86.5, 85.8, 75.9, 58.5, 55.6, 39.7, 30.7, 26.2; IR ($CHCl_3$, cm^{-1}): ν 2950, 1756, 1624, 1385, 1238; HRMS (ES): calcd for $C_{18}H_{19}ClN_2O_2$ [*M*]$^+$: 330.1135; found: 330.1135.

Allenyl β-Lactam 28f. From 500 mg (1.6 mmol) of alkynyl-β-lactam **26f**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **28f** (261 mg, 50%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.23 (d, 1H, *J* = 8.9 Hz), 7.06 (d, 1H, *J* = 2.3 Hz), 6.90 (dd, 1H, *J* = 8.9, 2.5 Hz), 6.48 (s, 1H), 5.05 (m, 1H), 5.03 (d, 1H, *J* = 4.4 Hz), 4.79 (d, 1H, *J* = 4.5 Hz), 4.72 (m, 2H), 3.90 (s, 3H), 3.73 (s, 3H), 3.68 (m, 1H), 3.20 (s, 3H), 3.15 (m, 1H), 2.24 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 208.8, 166.9, 154.2, 133.8, 133.2, 127.5, 122.3, 109.8, 102.7, 102.2, 86.5, 85.8, 75.8, 58.4, 55.8, 55.6, 39.6, 30.6, 26.2; IR ($CHCl_3$, cm^{-1}): ν 2950, 1760, 1615, 1394, 1243; HRMS (ES): calcd for $C_{19}H_{22}N_2O_3$ [*M*]$^+$: 326.1630; found: 326.1630.

General Procedure for the Gold-Catalyzed Hydroarylation Reaction of β-Lactam-Tethered Allenyl Indoles 27. Preparation of Azeto-oxepino[4,5-*b*]indol-2-ones 29. The appropriate allene **27** (1.0 mmol) was added to a stirred solution of [AuClIPr] (0.05 mmol) and $AgSbF_6$ (0.05 mmol) in 1,2-dichloroethane (13.0 mL) under argon. The resulting mixture was stirred at room temperature until disappearance of the starting material (TLC). After filtration through a pad of Celite, the mixture was extracted with ethyl acetate (3 x 5 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate or dichloromethane/ethyl acetate mixtures gave analytically pure tetracyclic compounds **29**.

Tetracycle 29a. From 85 mg (0.24 mmol) of allene **27a**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **29a** (61 mg, 72%) as a colorless solid; mp 142–143 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 8.02 (d, 1H, *J* = 8.0 Hz), 7.28 (m, 4H), 7.21 (m, 3H), 7.08 (td, 1H, *J* = 7.3, 1.4 Hz), 5.73 (m, 1H), 5.49 (d, 1H, *J* = 5.0 Hz), 5.32 (d, 1H, *J* = 16.6 Hz), 5.23 (dd, 1H, *J* = 10.0, 1.3 Hz), 5.01 (d, 1H, *J* = 5.0 Hz), 4.90 (d, 1H, *J* = 15.8 Hz), 4.19 (m, 2H), 4.14 (d, 1H, *J* = 15.8 Hz), 3.98 (m, 1H), 3.35 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 167.7, 137.9, 137.4, 135.2, 129.3, 128.9 (2C), 128.0, 127.7, 127.6 (2C), 122.8, 121.1, 119.3, 117.6, 115.1, 109.2, 87.5, 70.5, 54.7, 44.6, 43.9, 29.8; IR ($CHCl_3$, cm^{-1}): ν 2933, 1751, 1132, 927, 743, 700; HRMS (ES): calcd for $C_{23}H_{22}N_2O_2$ [*M*]$^+$: 358.1681; found: 358.1694.

Tetracycle 29b. From 33 mg (0.085 mmol) of allene **27b**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **29b** (23 mg, 68%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.67 (d, 1H, *J* = 8.0 Hz), 7.21 (m, 2H), 7.09 (m, 3H), 6.82 (d, 2H, *J* = 8.6 Hz), 5.73 (m, 1H), 5.46 (d, 1H, *J* = 5.0 Hz), 5.32 (d, 1H, *J* = 17.0 Hz), 5.23 (d, 1H, *J* = 10.1 Hz), 4.99 (d, 1H, *J* = 5.0 Hz), 4.84 (d, 1H, *J* = 15.6 Hz), 4.18 (m, 2H), 4.07 (d, 1H, *J* = 15.6 Hz), 3.97 (m, 1H), 3.77 (s, 3H), 3.37 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 167.6, 159.3, 137.8, 137.4, 128.9 (2C), 127.8, 127.5, 127.1, 122.7, 121.0, 119.3, 117.5, 115.0, 114.3 (2C), 109.1, 87.4, 70.4, 55.3, 54.5, 44.0, 43.9, 29.8; IR ($CHCl_3$, cm^{-1}): ν 2935, 1750, 1134, 929, 735; HRMS (ES): calcd for $C_{24}H_{24}N_2O_3$ [*M*]$^+$: 388.1787; found: 388.1764.

Tetracycle 29c. From 59 mg (0.16 mmol) of allene **27c**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **29c** (27 mg,

63%) as a colorless solid; mp 109–110 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.70 (d, 1H, *J* = 7.9 Hz), 7.34 (m, 2H), 7.19 (d, 2H, *J* = 9.1 Hz), 7.14 (m, 1H), 6.82 (d, 2H, *J* = 9.1 Hz), 5.75 (m, 1H), 5.51 (d, 1H, *J* = 5.1 Hz), 5.41 (d, 1H, *J* = 5.1 Hz), 5.27 (d, 1H, *J* = 17.1 Hz), 5.17 (dd, 1H, *J* = 10.1, 1.3 Hz), 4.27 (m, 1H), 4.23 (m, 1H), 4.06 (m, 1H), 3.77 (s, 3H), 3.74 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 165.0, 157.8, 138.0, 137.2, 129.6, 127.9, 127.6, 123.0, 122.1 (2C), 121.0, 119.6, 117.5, 115.5, 114.6 (2C), 109.5, 87.0, 69.9, 57.0, 55.4, 43.6, 30.6; IR ($CHCl_3$, cm^{-1}): ν 2933, 1755, 1129, 929, 738; HRMS (ES): calcd for $C_{23}H_{22}N_2O_3$ [*M*]$^+$: 374.1630; found: 374.1637.

Tetracycle 29d. From 131 mg (0.30 mmol) of allene **27d**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **29d** (107 mg, 82%) as a colorless solid; mp 155–156 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.57 (d, 1H, *J* = 8.0 Hz), 7.33 (d, 2H, *J* = 8.5 Hz), 7.17 (m, 1H), 7.14 (t, 1H, *J* = 7.6 Hz), 6.99 (m, 1H), 6.98 (d, 2H, *J* = 8.2 Hz), 5.63 (m, 1H), 5.39 (d, 1H, *J* = 5.0 Hz), 5.21 (d, 1H, *J* = 16.9 Hz), 5.15 (dd, 1H, *J* = 10.2, 1.5 Hz), 4.91 (d, 1H, *J* = 5.1 Hz), 4.68 (d, 1H, *J* = 15.9 Hz), 4.10 (m, 1H), 4.07 (m, 1H), 4.05 (d, 1H, *J* = 15.8 Hz), 3.85 (m, 1H), 3.31 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 167.7, 137.8, 137.1, 134.3, 132.0 (2C), 129.2 (2C), 127.4, 127.3, 122.9, 121.9, 121.0, 119.4, 117.7, 115.1, 109.1, 87.5, 70.5, 57.0, 54.8), 44.0, 43.9, 29.9; IR ($CHCl_3$, cm^{-1}): ν 2935, 1753, 1129, 924, 732; HRMS (ES): calcd for $C_{23}H_{21}BrN_2O_2$ [*M*]$^+$: 436.0786; found: 436.0804.

Tetracycle 29e. From 53 mg (0.16 mmol) of allene **27e**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **29e** (47 mg, 89%) as a colorless solid; mp 143–144 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.69 (d, 1H, *J* = 8.1 Hz), 7.29 (m, 2H), 7.10 (td, 1H, *J* = 7.1, 1.9 Hz), 5.73 (m, 1H), 5.43 (d, 1H, *J* = 5.0 Hz), 5.33 (d, 1H, *J* = 16.5 Hz), 5.22 (d, 1H, *J* = 10.1 Hz), 5.05 (d, 1H, *J* = 5.1 Hz), 4.19 (m, 1H), 4.16 (m, 1H), 3.96 (m, 1H), 3.78 (s, 3H), 3.26 (dd, 1H, *J* = 14.1, 8.2 Hz), 3.04 (dd, 1H, *J* = 14.1, 6.4 Hz), 1.70 (m, 1H), 0.87 (d, 3H, *J* = 2.3 Hz), 0.84 (d, 3H, *J* = 2.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 167.6, 137.8, 137.2, 128.5, 127.5, 122.8, 121.2, 119.3, 117.7, 114.9, 109.2, 87.2, 70.4, 56.0, 49.7, 44.0, 30.1, 27.8, 20.3, 20.2; IR ($CHCl_3$, cm^{-1}): ν 2935, 1752, 1130, 925, 732; HRMS (ES): calcd for $C_{20}H_{24}N_2O_2$ [*M*]$^+$: 324.1838; found: 324.1832.

General Procedure for the Gold-Catalyzed Hydroarylation/N1–C4 β-Lactam Cleavage of β-Lactam-Tethered Allenyl Indoles 27. Preparation of 1,6-Dihydro-2*H*-oxepino[4,5-*b*]indole-4-carboxamides 30. The appropriate allene **27** (1.0 mmol) was added to a stirred solution of [AuClIPr] (0.05 mmol) and $AgSbF_6$ (0.05 mmol) in 1,2-dichloroethane (13.0 mL) under argon. The resulting mixture was stirred at room temperature (**27f**) or at 84 ºC (**27a–e**), until disappearance of the starting material (TLC). After filtration through a pad of Celite, the mixture was extracted with ethyl acetate (3 x 5 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure tricyclic compounds **30**.

Tricycle 30a. From 85 mg (0.24 mmol) of allene **27a**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **30a** (51 mg, 60%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.52 (d, 1H, *J* = 7.9 Hz), 7.36 (m, 4H), 7.33 (m, 3H), 7.23 (s, 1H), 7.15 (br s, 1H), 7.10 (t, 1H, *J* = 7.9 Hz), 6.02 (m, 1H), 5.15 (d, 1H, *J* = 10.1 Hz), 5.06 (d, 1H, *J* = 17.0 Hz), 4.67 (dd, 1H, *J* = 11.1, 3.3 Hz), 4.57 (m, 2H), 4.19 (m, 1H), 4.04 (dd, 1H, *J* = 11.1, 1.3 Hz), 3.83 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 162.9, 148.0, 138.1, 137.7, 130.7, 128.7 (2C), 128.1, 127.6 (2C), 127.0, 122.9, 119.7, 118.6, 117.0, 116.8, 109.4, 101.0, 72.9, 43.8, 43.2, 29.6; IR ($CHCl_3$, cm^{-1}): ν 3401,

2925, 1682, 1522, 1361, 755, 700; HRMS (ES): calcd for $C_{23}H_{22}N_2O_2$ $[M]^+$: 358.1681; found: 358.1680.

Tricycle 30b. From 40 mg (0.10 mmol) of allene **27b**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **30b** (21 mg, 53%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.55 (d, 1H, *J* = 7.9 Hz), 7.33 (d, 2H, *J* = 8.6 Hz), 7.32 (m, 1H), 7.29 (m, 1H), 7.28 (m, 1H), 7.13 (td, 1H, *J* = 7.4, 1.3 Hz), 7.14 (br s, 1H), 6.93 (d, 2H, *J* = 8.6 Hz), 6.04 (m, 1H), 5.18 (d, 1H, *J* = 10.1 Hz), 5.09 (d, 1H, *J* = 17.0 Hz), 4.69 (dd, 1H, *J* = 11.1, 3.4 Hz), 4.54 (m, 2H), 4.21 (m, 1H), 4.05 (dd, 1H, *J* = 11.1, 1.3 Hz), 3.85 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 162.7, 159.1, 148.1, 137.7, 137.5, 130.6, 130.2, 129.4 (2C), 126.9, 122.8, 119.6, 118.5, 116.8, 116.7, 114.0 (2C), 109.4, 100.9, 72.8, 55.3, 43.2, 43.1, 29.5; IR ($CHCl_3$, cm^{-1}): ν 3400, 2928, 1685, 1528, 1403, 735; HRMS (ES): calcd for $C_{24}H_{24}N_2O_3$ $[M]^+$: 388.1787; found: 388.1798.

Tricycle 30c. From 71 mg (0.19 mmol) of allene **27c**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **30c** (48 mg, 67%) as a colorless solid; mp 148–149 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 8.51 (s, 1H), 7.56 (d, 2H, *J* = 9.1 Hz), 7.50 (dt, 1H, *J* = 7.9, 0.9 Hz), 7.26 (m, 2H), 7.22 (m, 1H), 7.07 (td, 1H, *J* = 7.3, 1.3 Hz), 6.87 (d, 2H, *J* = 9.1 Hz), 6.03 (m, 1H), 5.16 (dt, 1H, *J* = 10.0, 1.3 Hz), 5.05 (dt, 1H, *J* = 17.0, 1.4 Hz), 4.75 (dd, 1H, *J* = 11.1, 3.3 Hz), 4.19 (m, 1H), 4.07 (dd, 1H, *J* = 11.1, 1.4 Hz), 3.78 (s, 3H), 3.77 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 160.4, 156.4, 148.0, 137.7, 137.6, 130.8, 130.6, 126.9, 123.0, 121.4 (2C), 119.7, 118.7, 117.1, 117.0, 114.2 (2C), 109.5, 101.4, 73.0, 55.4, 43.1, 29.5; IR ($CHCl_3$, cm^{-1}): ν 3398, 2920, 1678, 1530, 1354, 736; HRMS (ES): calcd for $C_{23}H_{22}N_2O_3$ $[M]^+$: 374.1630; found: 374.1630.

Tricycle 30d. From 72 mg (0.17 mmol) of allene **27d**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **30d** (29 mg, 40%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 8.55 (d, 1H, *J* = 8.0 Hz), 7.52 (d, 2H, *J* = 8.5 Hz), 7.34 (t, 1H, *J* = 8.2 Hz), 7.31 (m, 1H), 7.29 (m, 1H), 7.28 (d, 2H, *J* = 8.5 Hz), 7.21 (m, 1H), 7.14 (t, 1H, *J* = 7.3 Hz), 6.04 (m, 1H), 5.20 (dt, 1H, *J* = 10.1, 1.3 Hz), 5.10 (dt, 1H, *J* = 17.0, 1.5 Hz), 4.72 (dd, 1H, *J* = 11.1, 3.4 Hz), 4.60 (dd, 1H, *J* = 14.9, 6.1 Hz), 4.52 (dd, 1H, *J* = 14.9, 6.0 Hz), 4.23 (m, 1H), 4.07 (dd, 1H, *J* = 11.1, 1.3 Hz), 3.86 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 163.0, 147.7, 137.6, 137.6, 137.2, 131.8 (2C), 130.5, 129.7 (2C), 126.9, 122.9, 121.4, 119.7, 118.6, 117.0, 116.9, 109.4, 101.1, 72.8, 43.1, 43.1, 29.6; IR ($CHCl_3$, cm^{-1}): ν 3390, 2928, 1682, 1526, 1359, 747; HRMS (ES): calcd for $C_{23}H_{21}BrN_2O_2$ $[M]^+$: 436.0786; found: 436.0774.

Tricycle 30e. From 46 mg (0.14 mmol) of allene **27e**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **30e** (26 mg, 58%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.52 (d, 1H, *J* = 7.9 Hz), 7.31 (d, 1H, *J* = 8.2 Hz), 7.24 (td, 1H, *J* = 7.6, 1.1 Hz), 7.20 (s, 1H), 7.10 (td, 1H, *J* = 7.4, 1.3 Hz), 6.92 (t, 1H, *J* = 5.5 Hz), 6.03 (m, 1H), 5.17 (dt, 1H, *J* = 10.1, 1.3 Hz), 5.08 (dt, 1H, *J* = 17.1, 1.4 Hz), 4.71 (dd, 1H, *J* = 11.1, 3.4 Hz), 4.20 (m, 1H), 4.06 (dd, 1H, *J* = 11.1, 1.4 Hz), 3.81 (s, 3H), 3.23 (m, 2H), 1.88 (m, 1H), 0.99 (s, 3H), 0.84 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 162.9, 148.3, 137.7, 137.5, 130.7, 126.9, 122.7, 119.6, 118.5, 116.8, 116.6, 109.4, 100.6, 72.8, 47.0, 43.1, 29.5, 28.6, 20.2 (2C); IR ($CHCl_3$, cm^{-1}): ν 3398 (NH), 2930, 1685, 1524, 1369; HRMS (ES): calcd for $C_{20}H_{24}N_2O_2$ $[M]^+$: 324.1838; found: 324.1843.

Tricycle 30f. From 30 mg (0.09 mmol) of allene **27f**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound **30f** (29 mg, 98%) as a colorless solid; mp 181–182 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 8.57 (s, 1H), 7.63 (d, 2H, *J* = 7.6 Hz), 7.48 (d, 1H, *J* = 7.9 Hz), 7.28 (m, 4H), 7.21 (s, 1H), 7.07 (m, 2H), 6.02 (m, 1H), 5.15 (dt, 1H, *J* = 10.0, 1.4 Hz), 5.04 (dt, 1H, *J* = 17.0, 1.4 Hz), 4.76 (dd, 1H, *J*

= 11.1, 3.3 Hz), 4.19 (m, 1H), 4.07 (dd, 1H, *J* = 11.1, 1.5 Hz), 3.78 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 160.6, 147.8, 137.7, 137.6, 130.6, 129.0 (2C), 126.9, 124.4, 123.1, 119.8 (2C), 119.7, 118.7, 117.3, 117.0, 109.5, 101.7, 73.0, 55.4, 43.1, 29.6; IR ($CHCl_3$, cm^{-1}): ν 3397, 2930, 1684, 1523, 1353, 754, 701; HRMS (ES): calcd for $C_{22}H_{20}N_2O_2$ [*M*]$^+$: 344.1525; found: 344.1518.

General Procedure for the Gold-Catalyzed Hydroarylation of β-Lactam-Tethered Allenyl Indoles 28. Preparation of Tetrahydroazeto-azocino[3,4-*b*]indol-2-ones 31 and Hexahydroazeto-azepino[3,4-*b*]indol-2-ones 32. The appropriate allene **28** (1.0 mmol) was added to a stirred solution of [AuClIPr] (0.05 mmol) and $AgSbF_6$ (0.05 mmol) in 1,2-dichloroethane (13.0 mL) under argon. The resulting mixture was stirred at 90 ºC under μwave irradiation until disappearance of the starting material (TLC). After filtration through a pad of Celite, the mixture was extracted with ethyl acetate (3 x 5 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure tetracyclic compounds **31** and **32**.

Tetracycle 31a. From 58 mg (0.21 mmol) of allene **28a**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **31a** (34 mg, 59%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.60 (d, 1H, *J* = 7.8 Hz), 7.28 (d, 1H, *J* = 7.3 Hz), 7.22 (td, 1H, *J* = 8.1, 1.2 Hz), 7.13 (td, 1H, *J* = 7.3, 1.4 Hz), 6.08 (m, 1H), 5.34 (m, 1H), 5.07 (d, 1H, *J* = 4.2 Hz), 4.92 (d, 1H, *J* = 4.4 Hz), 4.77 (d, 1H, *J* = 18.5 Hz), 3.98 (dd, 1H, *J* = 14.7, 7.4 Hz), 3.70 (s, 3H), 3.61 (d, 1H, *J* = 18.5 Hz), 3.35 (m, 1H), 3.33 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 167.4, 136.9, 131.6, 129.5, 127.1, 123.1, 121.8, 119.3, 115.3, 115.3, 108.8, 87.8, 58.3 (2C), 42.6, 29.9, 20.6; IR ($CHCl_3$, cm^{-1}): ν 2935, 1750, 1132, 929; HRMS (ES): calcd for $C_{17}H_{18}N_2O_2$ [*M*]$^+$: 282.1368; found: 282.1372.

Tetracycle 31b. From 85 mg (0.27 mmol) of allene **28b**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **31b** (59 mg, 70%) as a colorless solid; mp 158–159 ºC; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.54 (dd, 1H, *J* = 1.7, 0.7 Hz), 7.16 (d, 1H, *J* = 0.6 Hz), 7.15 (d, 1H, *J* = 1.7 Hz), 6.03 (m, 1H), 5.35 (m, 1H), 5.04 (d, 1H, *J* = 4.5 Hz), 4.91 (d, 1H, *J* = 4.4 Hz), 4.76 (d, 1H, *J* = 18.4 Hz), 3.95 (dd, 1H, *J* = 14.8, 7.2 Hz), 3.67 (s, 3H), 3.61 (d, 1H, *J* = 18.3 Hz), 3.34 (s, 3H), 3.23 (dd, 1H, *J* = 14.8, 9.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 167.2, 135.2, 131.3, 131.1, 128.0, 125.1, 123.3, 122.0, 117.5, 114.9, 109.8, 85.7, 58.4, 58.1, 42.6, 30.1, 20.6; IR ($CHCl_3$, cm^{-1}): ν 2939, 1753, 1138, 933; HRMS (ES): calcd for $C_{17}H_{17}ClN_2O_2$ [*M*]$^+$: 316.0979; found: 316.0990.

Tetracycle 31c. From 49 mg (0.16 mmol) of allene **28c**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **31c** (26 mg, 53%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.16 (d, 1H, *J* = 8.9 Hz), 7.02 (d, 1H, *J* = 2.3 Hz), 6.87 (dd, 1H, *J* = 8.8, 2.4 Hz), 6.09 (m, 1H), 5.34 (m, 1H), 5.05 (br s, 1H), 4.91 (br s, 1H), 4.75 (d, 1H, *J* = 18.5 Hz), 3.95 (dd, 1H, *J* = 14.9, 7.3 Hz), 3.88 (s, 3H), 3.67 (s, 3H), 3.61 (m, 1H), 3.32 (s, 3H), 3.27 (dd, 1H, *J* = 14.7, 9.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 167.4, 154.1, 132.2, 131.4, 130.0, 127.2, 123.2, 114.8, 112.1, 109.6, 99.8, 85.7, 58.4 (2C), 56.0), 42.6, 30.1, 20.7; IR ($CHCl_3$, cm^{-1}): ν 2939, 1752, 1127, 945; HRMS (ES): calcd for $C_{18}H_{20}N_2O_3$ [*M*]$^+$: 312.1474; found: 312.1481.

Tetracycle 32a. From 35 mg (0.12 mmol) of allene **28d**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **32a** (12 mg, 35%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.48 (d, 1H, *J* = 7.9 Hz), 7.29 (m, 1H), 7.22 (td, 1H, *J* = 8.2, 1.2 Hz), 7.11 (td, 1H, *J* = 7.3, 1.1 Hz), 6.09 (m, 1H), 5.17 (dt, 1H, *J* = 10.1, 2.7 Hz), 5.15 (m, 1H), 5.05 (dt, 1H, *J* = 17.0, 1.6 Hz), 4.96 (dd, 1H, *J* = 4.5,

1.6 Hz), 4.15 (m, 1H), 4.06 (m, 1H), 3.67 (s, 3H), 3.38 (s, 3H), 3.28 (m, 1H), 2.24 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 166.4, 159.7, 138.4, 131.9, 127.3, 121.7, 119.2, 118.0, 116.8, 115.3, 115.5, 108.8, 85.9, 57.9, 56.1, 37.9, 36.9, 30.5, 29.7; IR ($CHCl_3$, cm^{-1}): ν 2940, 1748, 1129, 930; HRMS (ES): calcd for $C_{18}H_{20}N_2O_2$ $[M]^+$: 296.1525; found: 296.1531.

Tetracycle 32b. From 39 mg (0.12 mmol) of allene **28e**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **32b** (13 mg, 33%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.42 (dd, 1H, *J* = 1.8, 0.6 Hz), 7.18 (d, 1H, *J* = 0.6 Hz), 7.17 (d, 1H, *J* = 1.9 Hz), 6.06 (m, 1H), 5.18 (dt, 1H, *J* = 10.1, 1.6 Hz), 5.12 (d, 1H, *J* = 4.5 Hz), 5.03 (dt, 1H, *J* = 17.0, 1.6 Hz), 4.94 (dd, 1H, *J* = 4.5, 1.6 Hz), 4.10 (m, 1H), 3.97 (m, 1H), 3.64 (s, 3H), 3.39 (s, 3H), 3.25 (m, 1H), 2.22 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 166.3, 138.1, 135.4, 133.4, 128.3, 125.1, 121.9, 117.6, 117.1, 115.2, 109.8, 85.9, 58.0, 56.0, 37.9, 36.9, 31.7, 30.7; IR ($CHCl_3$, cm^{-1}): ν 2947, 1751, 1133, 928; HRMS (ES): calcd for $C_{18}H_{19}ClN_2O_2$ $[M]^+$: 330.1135; found: 330.1135.

Tetracycle 32c. From 102 mg (0.31 mmol) of allene **28f**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **32c** (37 mg, 36%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.19 (d, 1H, *J* = 8.6 Hz), 6.90 (m, 1H), 6.88 (dd, 1H, *J* = 8.6, 2.5 Hz), 6.08 (m, 1H), 5.17 (dt, 1H, *J* = 10.1, 1.5 Hz), 5.12 (d, 1H, *J* = 4.4 Hz), 5.06 (dt, 1H, *J* = 17.0, 1.7 Hz), 4.95 (dd, 1H, *J* = 4.5, 1.5 Hz), 4.12 (m, 1H), 3.99 (m, 1H), 3.85 (s, 3H), 3.63 (s, 3H), 3.36 (s, 3H), 3.27 (m, 1H), 2.24 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 166.4, 154.1, 138.3, 132.5, 132.4, 127.6, 116.8 117.1, 114.9, 111.7, 109.5, 100.2, 85.9, 57.8, 56.1, 56.0, 37.9, 37.0, 31.8, 30.7; IR ($CHCl_3$, cm^{-1}): ν 2947, 1751, 1139, 926; HRMS (ES): calcd for $C_{19}H_{22}N_2O_3$ $[M]^+$: 326.1630; found: 326.1632.

VI.4. Notes and references

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VII. CAPÍTULO 4

VII.1. Stereoselective Synthesis of Strained Cage Compounds *via* Gold-Catalyzed Allene Functionalization

The diastereoselective synthesis of strained adducts that show cage-like structure has been accomplished directly from allenyl-β-lactams through gold catalysis.

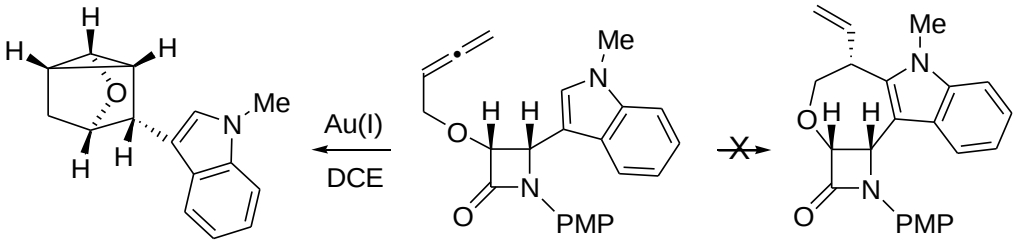
Chem. Commun. **2016**, *52*, 10265

VII.2. Communication

The last decade has witnessed dramatic growth in the number of reactions catalyzed by gold complexes.[1] On the other hand, allenes[2] and β-lactams[3] have independently shown interesting reactivities and selectivities. In particular, gold-based complexes are suitable catalysts for polycyclic azetidinone formation.[4] Herein, we present a novel an unanticipated reactivity in gold catalysis starting from 3-allenyl 4-aryl(alkenyl) β-lactams.

Allenyl-β-lactam **37a** was initially chosen to study the possibility of an allene–aryl coupling. The allene functionally of starting substrate **37a** efficiently reacted under gold catalysed conditions, but unexpectedly the 2-azetidinone ring also disappeared in the final product **38a**, which reveals a highly complex cage structure (Table VII.1). The reaction efficiency varied considerably depending on the ligand, counter-anion, and temperature. $AuCl_3$, AuCl, and [(PPh_3)AuOTf] all failed to catalyse this reaction (Table VII.1, entries 1–3). Our catalyst screening led to the identification of [AuClIPr]/$AgSbF_6$ as the most suitable promoter.

Among all the solvents examined, 1,2-dichloroethane (DCE) proved to be the best choice. The gold-catalysed reaction was sluggish at room temperature and after three days provided the product in a low yield (19%) (Table VII.1, entry 4). To our delight, the combined use of [IPrAuCl] (5 mol%) and $AgSbF_6$ (5 mol%) in refluxing DCE after 30 min resulted in an increased 75% yield for adduct **38a** (Table VII.1, entry 5). Applying microwave irradiation at 90^{o}C returned the best result, affording strained cage compound **38a** in 83% yield in just 10 min (Table VII.1, entry 6). The reaction of allene **37a** using Gagosz' catalyst [(Ph_3P)$AuNTf_2$] did not lead to complete consumption of starting **37a**, providing adduct **38a** in low yield (Table VII.1, entry 7). The yield could be improved neither by using [IPrAuNTf_2] nor [IPrAuOTf], nor [IPrAuCl]/$AgBF_4$ as catalysts (Table VII.1, entries 8–10).



38a **37a**

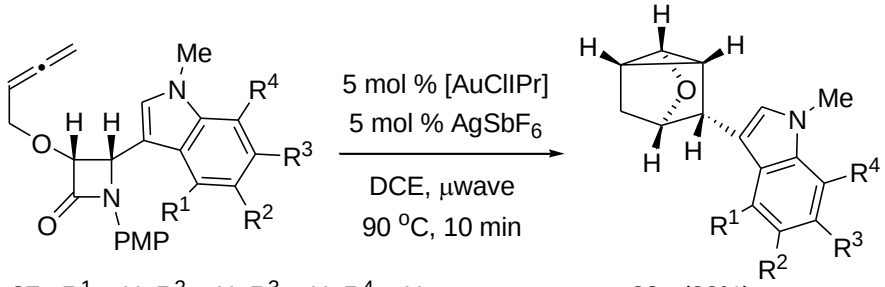
entry	catalyst	T (°C)	time (h)	yield (%)[a]
1	$AuCl_3$	20	24	–
2	AuCl	20	24	–
3	$[(PPh_3)AuCl]/AgOTf$	20	24	–
4	[AuClIPr][b]/$AgSbF_6$	20	72	**38a** (19)
5	[AuClIPr]/$AgSbF_6$	84	0.5	**38a** (75)
6	[AuClIPr]/$AgSbF_6$	90	0.16	**38a** (83)[c]
7	$[(Ph_3P)AuNTf_2]$	84	1.5	**38a** (12)
8	[AuClIPr]/$AgNTf_2$	84	0.5	**38a** (29)
9	[AuClIPr]/AgOTf	84	0.5	–
10	[AuClIPr]/$AgBF_4$	84	0.5	**38a** (67)

[a]Yield of pure, isolated product with correct analytical and spectral data. [b]IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [c]Reaction runs under microwave irradiation.

Table VII.1. Catalyst screening for the gold-catalysed unpredictable reaction of 3-allenyl 4-[(indol-3-yl)] 2-azetidinone **37a** to afford cage adduct **38a**. PMP = 4-$MeOC_6H_4$.

No advantage is gained from changing the 4-methoxyphenyl (PMP) substituent at N1 to a phenyl moiety, because the phenyl analogue was a poor participant.[5] Having the optimized conditions, we then studied the scope of the protocol by examining substitution on the indole moiety of the allenyl 4-indolyl β-lactams **37**. Introduction of substituents on the aryl ring of **37** did not influence the efficiency of the reaction. For example, substrates **37b** and **37c** lead directly to the corresponding adducts **38b** and **38c** in good yields after exposure to 5 mol% of [AuClIPr]/$AgSbF_6$ (Scheme VII.1). It was found that introduction of electron-donating groups at the 5-, 6-, and 7-positions of the indole ring was fully tolerated

(Scheme VII.1; **38d–f**). The single crystal XRD structure of nitro derivative **38c** unambiguously confirmed its strained oxa-cage nature (Figure VII.1).[6,7] Notably, five new contiguous stereogenic centers have been created in a totally diastereoselective fashion in just a single operation.



37a R^1 = H, R^2 = H, R^3 = H, R^4 = H — **38a** (83%)
37b R^1 = H, R^2 = Br, R^3 = H, R^4 = H — **38b** (64%)
37c R^1 = NO_2, R^2 = H, R^3 = H, R^4 = H — **38c** (85%)
37d R^1 = H, R^2 = MeO, R^3 = H, R^4 = H — **38d** (74%)
37e R^1 = H, R^2 = H, R^3 = H, R^4 = Me — **38e** (57%)
37f R^1 = H, R^2 = H, R^3 = iPr, R^4 = H — **38f** (60%)

Scheme VII.1. Synthesis of strained cage compounds **38a–f**.

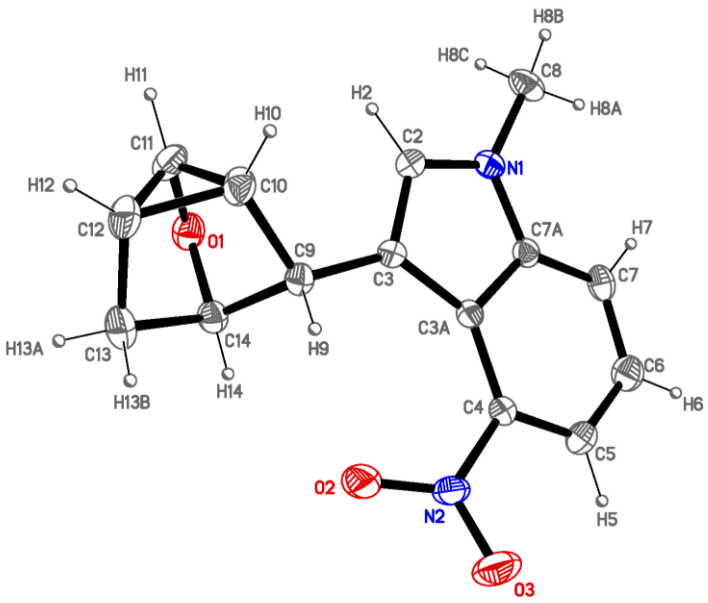
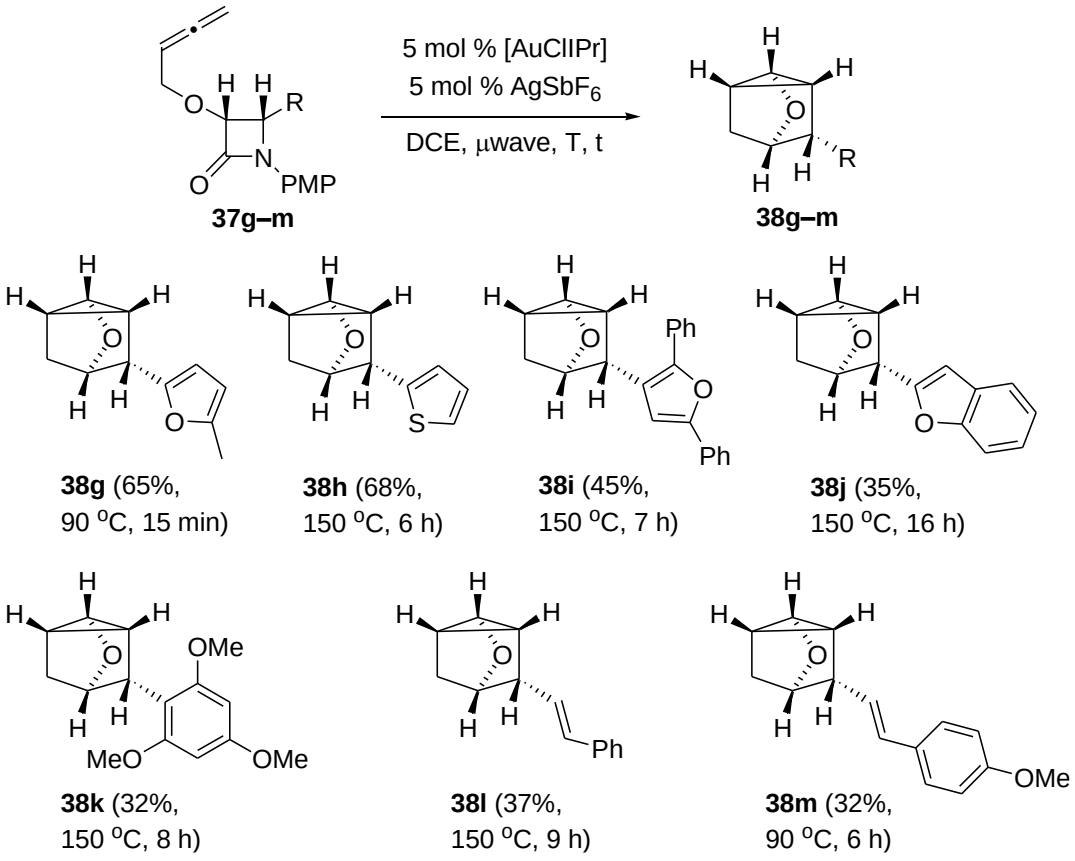


Figure VII.1. ORTEP drawing of 5-indolyl-3-oxatricyclo[2.2.1.$0^{2,6}$]heptane **38c**.

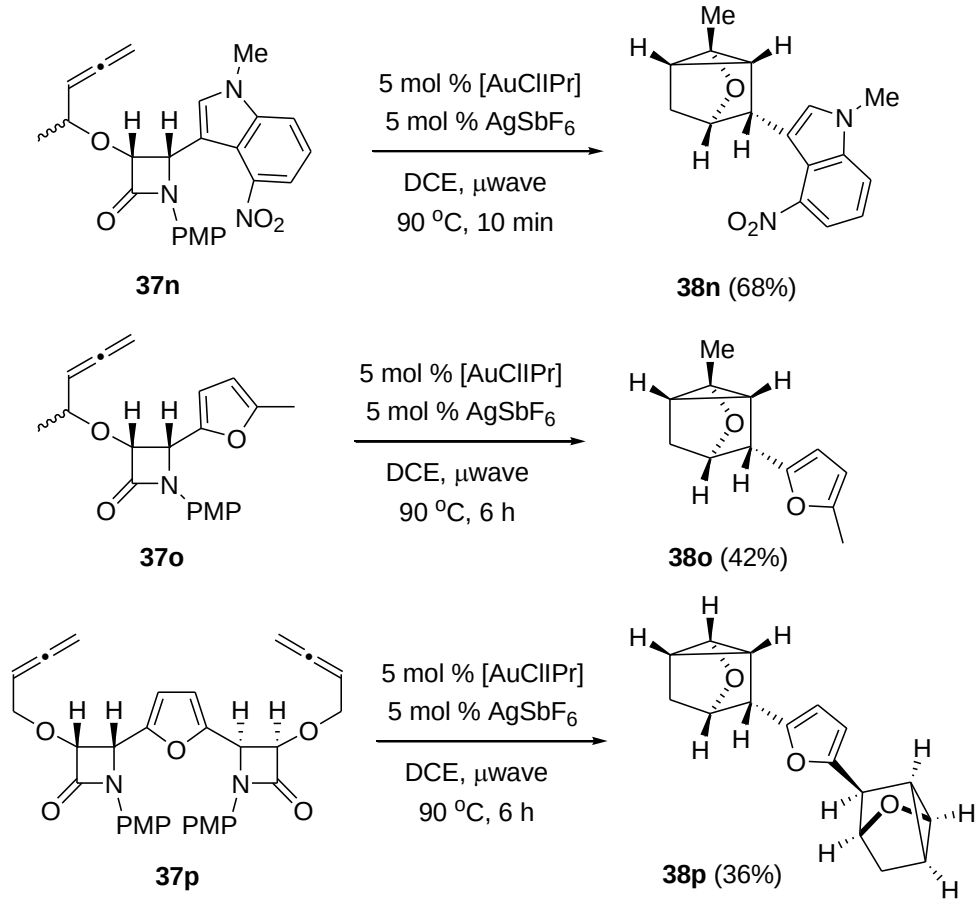
The construction of compounds bearing novel structures in a predictable and selective way is a major challenge in modern chemistry. In particular, the molecular

architecture of strained cage compounds **38** is appealing.[7] Towards this end, we set out to investigate the scope of this reaction by variation of the C4-substituent at the β-lactam ring. The electronic nature of the aromatic rings of precursors **37** did have a strong influence on the above reaction. For example, 3-allenyl 4-aryl β-lactams **37** possessing electron-withdrawing substituents, such as 4-nitrophenyl, or π-deficient heterocycles, such as pyridine, failed. We observed that a variety of hetaryl, aryl, and alkenyl moieties were well tolerated, because treatment of allenes **37g–m** with [AuClIPr]/$AgSbF_6$ in 1,2-dichloroethane under microwave irradiation gave the rearrangement reaction. The gold salt specifically promoted the generation of the desired cage adducts **38g–m** (Scheme VII.2). Complete conversion was observed by TLC and ^{1}H NMR analysis of the crude reaction mixtures of allenes **37**, and no side-products from competitive reactions were detected. Unfortunately, some decomposition was observed on sensitive cage adducts **38** during purification by flash chromatography, which may be responsible for the moderate isolated yields.



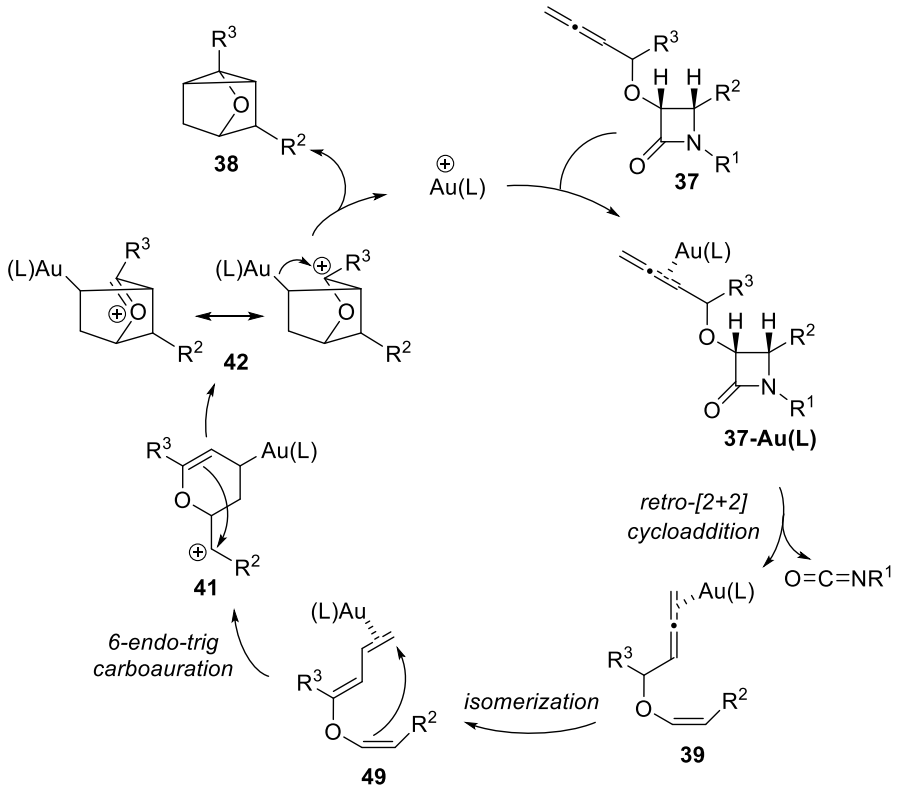
Scheme VII.2 Synthesis of strained cage compounds **38g–m**.

Branched allenes **37n** and **37o** were also well tolerated (Scheme VII.3). The methyl-substituted allene **37n** was converted into the constrained cage product **38n** in good yield while the reaction of its related derivative **37o** gave the corresponding adduct **38o** in moderate yield. Worthy of note, despite that precursors **37n** and **37o** were mixture of epimers that were not separated, both epimers at the methyl-substituted carbon converged in the formation of cage products **38n** and **38o**, which were formed as single isomers. The aim of the use of substrates **37n** and **37o** was double, namely, to allow for branched allenes to participate in the rearrangement as well as to obviate the need for a stereoselective precursor preparation. Our conditions were also effective for the two-fold reaction of bis(allenyl-β-lactam) **37p** (Scheme VII.3). This substrate provided in a totally selective fashion the desired bis(cage) adduct **38p** in moderate yield through a double reaction sequence.



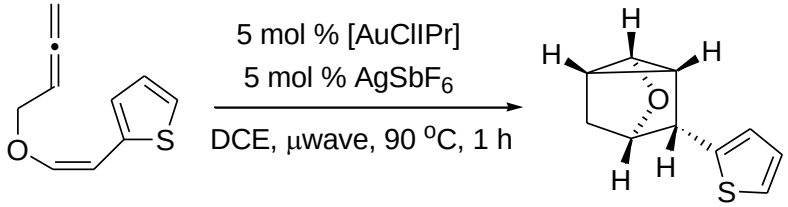
Scheme VII.3 Synthesis of methyl-substituted cage adducts **38n,o** and bis(cage) adduct **38p**.

A possible pathway for the gold-catalysed generation of cage compounds **38** is outlined in Scheme VII.4. Initially, the formation of a complex **37**-Au(L) through coordination of the gold salt to the internal allene double bond may be involved. Initially, (vinyloxy)buta-1,2-dienes **39** could be formed through a retro-[2+2] alkene–isocyanate cycloaddition.[8] Next, allene-diene isomerization could lead to gold-complexed conjugated dienes **40**.[9,10] This path must be driven by relief of the strain associated with the four-membered ring, on forming highly conjugated polyene intermediates, enol ethers **40**. Species **40** suffers an intramolecular chemo- and regioselective carbocyclization reaction to produce (3,4-dihydro-2*H*-pyran-4-yl)gold carbenium species **41**. Activation of the exocyclic methylene position by a delocalized benzylic-like carbocation can induce selectively a new carbocyclization to bicyclic cations **42**. Species **42** are stabilized by the electron pair of the α heteroatom, which would facilitate the intramolecular nucleophilic addition of the gold-bonded carbon to the ion moiety. The result of this carbocyclization is the formation of cage compounds **38** with concurrent regeneration of the gold catalyst (Scheme VII.4).



Scheme VII.4. Mechanistic explanation for the Au(I)-catalyzed synthesis of cage compounds **38** from allenyl-β-lactams **37**.

According to the above mechanism, cage compounds **38** could be obtained from (vinyloxy)buta-1,3-dienes **40** or from (vinyloxy)buta-1,2-dienes **39** (via isomerisation to dienyl-vinyl ethers **40** and further cyclization). To gain insight into the mechanism, a proposed intermediate, the previously unknown polyene (vinyloxy)buta-1,2-diene **39h**, was synthesized (see Supporting Information for details) and submitted to the standard conditions, resulting in formation of cage adduct **38h** in a yield of 45% (Scheme VII.5). This fact clearly confirmed the crucial use of stable and readily prepared allenyl-β-lactams as masked dienyl-vinyl ethers in gold catalysis.[11]



39h **38h** (45%)

Scheme VII.5 Preparation of strained cage compound **38h** through tris(cyclization) of (vinyloxy)buta-1,2-diene **39h** under gold catalysis.

Density Functional Theory (DFT) calculations[12] were carried out to gain more insight into the gold(I)-catalysed transformation of buta-1,2-dienes **39** into the cage compounds **38**. To this end, we explored the corresponding reaction profile involving the furyl-substituted buta-1,2-diene **1M** and the model [1,3-bis(methyl)-1,3-dihydro-2*H*-imidazol-2-ylidene]-Au^+ catalyst leading to the cage compound **2M** (Figure VII.2).

The process begins with the highly exergonic coordination of the allenyl moiety of **1M** to the gold(I) catalyst to form the π-complex **3M** (ΔG_R = –38.5 kcal/mol). From the data in Figure VII.2, this species readily isomerizes into the thermodynamically more stable 1,3-diene derivative **4M** (ΔG_R = –15.5 kcal/mol) in a transformation which is very likely mediated by the catalyst counteranion according to previously reported gold-catalysed allenyl-diene isomerizations.[9,10]

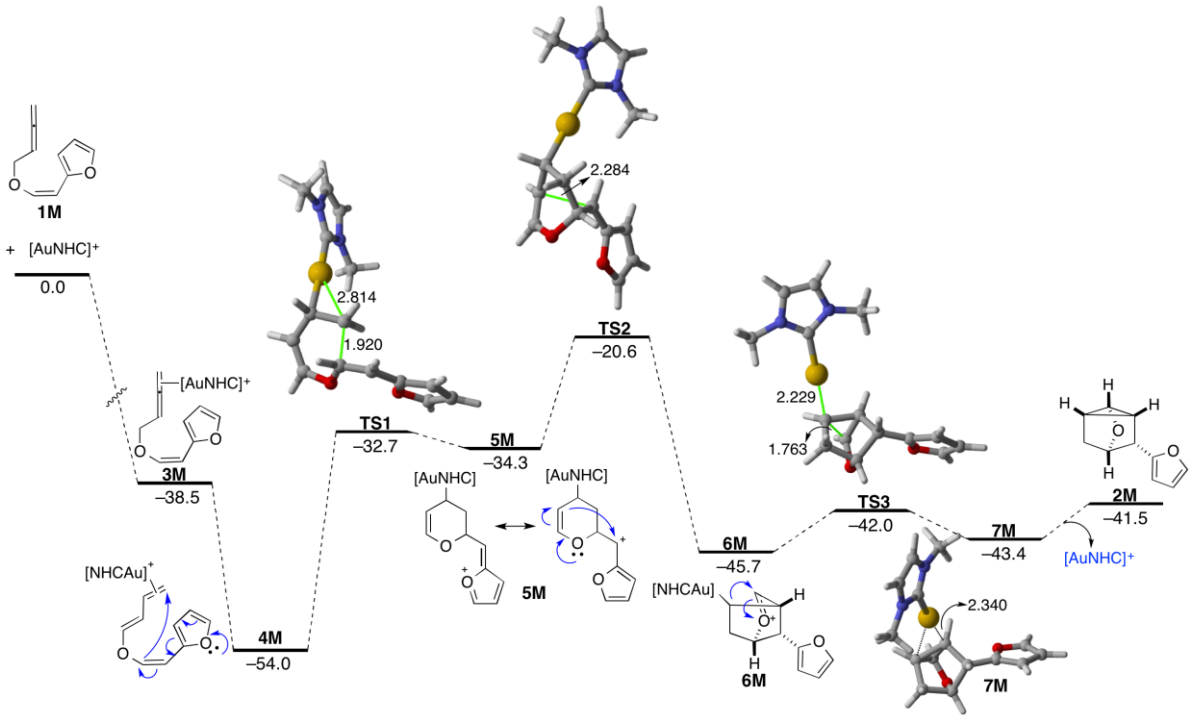


Figure VII.2 Computed profile for the gold(I)-catalysed transformation of allenyl derivative **3M** into cage-compound **2M**. Bond lengths and relative free energies (ΔG_{298}, computed at 298 K) are given in angstroms and kcal/mol, respectively. NHC = 1,3-bis(methyl)-1,3-dihydro-2*H*-imidazol-2-ylidene. All data have been computed at the PCM(dichloroethane)-B3LYP-D3/def2-TZVP//PCM(dichloroethane)-B3LYP-D3/def2-SVP level.

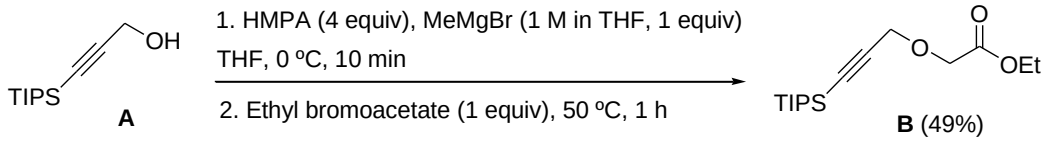
Intermediate **4M** experiences then a carbocyclization reaction leading to the carbocationic intermediate **5M** through transition state **TS1** ($\Delta G^{\neq}$ = 21.3 kcal/mol). This saddle point is associated with the formation of a new C–C bond and occurs in a regioselective manner from the nucleophilic attack of the carbon atom at the β-position of the furyl moiety to the distal CH_2 fragment of the diene. This finding provides further support to the experimental observation that only electron-rich aryl groups, which greatly increase the nucleophilicity of this β-carbon atom, are able to participate in the transformation. Carbenium intermediate **5M** evolves into oxacarbenium derivative **6M** via **TS2** ($\Delta G^{\neq}$ = 13.7 kcal/mol) in a highly exergonic reaction (ΔG_R = –25.1 kcal/mol). The saddle point **TS2** is associated with the formation of the second C–C bond as a result of the intramolecular nucleophilic addition of the carbon atom at the β-position of the oxygen atom (i.e. enol ether) to the benzylic-like carbocationic centre of **5M**. A new intramolecular carbocyclization

reaction derived from the easy ($\Delta G^{\neq}$ = 3.7 kcal/mol) nucleophilic attack from the carbon atom directly attached to the metal fragment to the carbon atom of the oxacarbenium moiety of **6M** via **TS3** finish the process. This reaction step results in the formation of the cage-compound **7M** where the gold(I)-catalyst is only weakly bonded to the cyclopropyl moiety. Final release of the catalyst would produce the observed tricyclic compound **2M** regenerating the catalyst. Therefore, our DFT calculations suggest that the transformation of allenyl-derivatives **39**, readily formed from the fragmentation of the corresponding β-lactams **37**, into the observed cage-compounds **38** involves an initial isomerization reaction to the thermodynamically more stable 1,3-butadiene coordinated Au(I)-complexes followed by three consecutive intramolecular carbocyclization reactions.

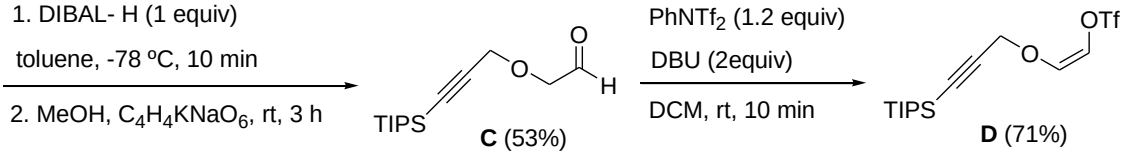
In conclusion, the diastereoselective synthesis of strained adducts which show cage-like structure has been accomplished directly from allenyl-β-lactams through gold catalysis. Both experimental results and DFT calculations support the involvement of (vinyloxy)buta-1,2-diene intermediates readily formed upon fragmentation of the β-lactam ring.

VII.3. Experimental Section

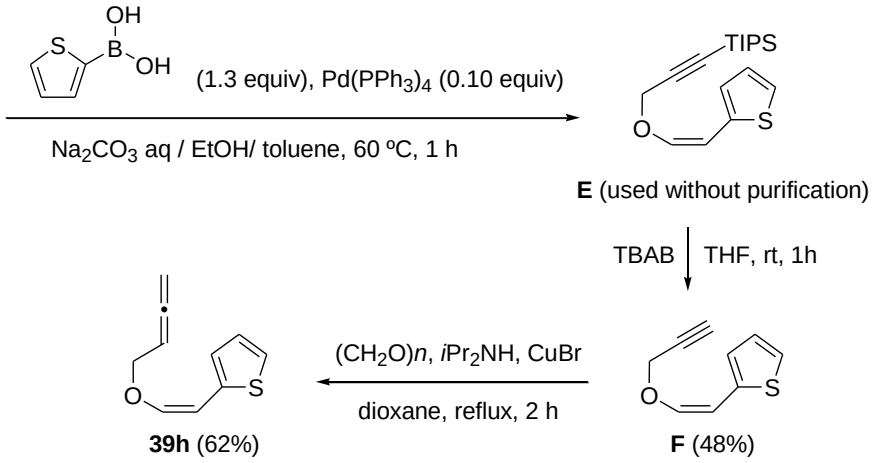
General Methods: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe or Varian VRX-300S. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{13}C, 76.9 ppm). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electrospray mode (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. All commercially available compounds were used without further purification.



compound **A** was prepared in a three-step sequence from propargyl alcohol as reported in Le. C. M.; Menzies, P. J. C.; Petrone, D. A.; Lautens, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 254



compound **D** was prepared according to a literature procedure: F.; Nakano, T.; Soeta, T.; Endo, K.; Ukaji, T. *J. Org. Chem.* **2015**, *80*, 5696

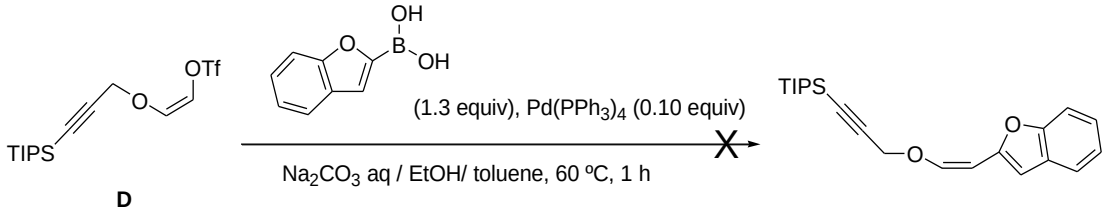


Scheme VII.S1. Synthesis of (vinyloxy)buta-1,2-diene **39h**.

Preparation of (*Z*)-2-[2-(prop-2-ynyloxy)vinyl]thiophene F. To a solution of triflate **D** (354, 0.92 mmol) in toluene (15 mL) and EtOH (2.5 mL) was added 2 M aq solution of Na_2CO_3 (15 mL). After $Pd(PPh_3)_4$ (106 mg, 0.09 mmol, 10 mol %) and 2-thienylboronic acid (198 mg, 1.55 mmol) were added, the reaction mixture was stirred at 60 °C for 1 h under argon atmosphere. The reaction mixture was cooled to room temperature and insoluble substance was filtered off through a pad of Celite. The aqueous layer of the filtrate was separated and extracted with Et_2O. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and solvent was evaporated. The crude product, which contained (*Z*)-triisopropyl(3-(2-(thiophen-2-yl)vinyloxy)prop-1-ynyl)silane **E**, was used for next reaction without further purification.

Tetra-*n*-butylammonium fluoride (1.0 equiv, THF solution 1M) was added to the crude residue containing 318 mg (0.99 mmol) of (*Z*)-triisopropyl(3-(2-(thiophen-2-yl)vinyloxy)prop-1-ynyl)silane **E** solved in THF (4 mL). After being stirred for 1 h at room temperature, the solution was diluted with ether. The organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated under reduced pressure.Flash chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **F** (78 mg, 48%) as a colorless oil;^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.19 (d, 1H, *J* = 5.1 Hz, Ar), 7.04 (d, 1H, *J* = 3.5 Hz, Ar), 6.97 (dd, 1H, *J* = 5.1, 3.7 Hz, Ar), 6.32 (d, 1H, *J* = 6.4 Hz, =CH), 5.78 (d, 1H, *J* = 6.4 Hz, =CH), 4.60 (d, 2H, *J* = 2.5 Hz, OCH_2), 2.55 (t, 1H, *J* = 2.5 Hz, ≡CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 142.3 (=CH), 137.6, 126.3 (Ar, CH), 125.3 (Ar, CH), 124.5 (Ar, CH), 102.4 (=CH), 78.3, 75.8 (≡CH), 59.6 (OCH_2); IR ($CHCl_3$): ν = 2940, 1650, 1359, 695, 666 cm^{-1}; HRMS (ES): calcd for $C_9H_9OS[M]^+$: 165.0374; found: 165.0372.

The reactions of two new (vinyloxy)buta-1,2-dienes **39** (**39g** and **39j**) were attempted. Unfortunately, the coupling step between enol triflate **D** and (5-methylfuran-2-yl)boronic acid or benzofuran-2-ylboronic acid were unproductive. The reaction of **D** with (5-methylfuran-2-yl)boronic acid was a complete mess under different reaction conditions. Also, the coupling of **D** with benzofuran-2-ylboronic acid was not very competent. After column chromatography we can isolate two fractions: The more polar compound was a clean product with a structure different to the desired (Z)-(3-((2-(benzofuran-2-yl)vinyl)oxy)prop-1-yn-1-yl)triisopropylsilane, while the more polar fraction was a mixture of various products. Consequently, it may be inferred that the synthesis of enol ether derivatives **39** is not trivial and our β-lactam based protocol is a more promising alternative.



D

Cu-Catalyzed Reaction of β-Lactam-Tethered Alkynes and (*Z*)-2-[2-(Prop-2-ynyloxy)vinyl]thiophene F. General Procedure for the Preparation of β-Lactam-Tethered Allenes 37a–p and (Vinyloxy)buta-1,2-diene 39h. A well stirred solution of$(CH_2O)_n$ (0.5 mmol), CuI (0.1 mmol), the appropriate alkyne (0.2 mmol), and *N*,*N*-diisopropylethylamine (Hüning's base) (0.36 mmol) in dioxane (1 mL) was refluxed under argon atmosphere. When the reaction was complete as monitored by TLC, it was cooled to RT. Water (5 mL) was added before being extracted with ethyl acetate(3 x 15 mL). The organic phase was washed with water (2 x 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds **37**. Spectroscopic and analytical data for allenes **37** follow.

β-Lactam-Tethered Allene 37a. From 91 mg (0.25 mmol) of the corresponding β-lactam-tethered alkyne, and after flash chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **37a** (58 mg, 61%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ= 7.82 (d, 1H, *J* = 8.0 Hz, ArH), 7.46 (d, 2H, *J* = 8.9 Hz, ArH), 7.45 (m, 1H, ArH), 7.38 (t, 1H, *J* = 7.4 Hz, ArH), 7.29 (m, 1H, ArH), 7.27 (s, 1H, ArH), 6.86 (d, 2H, *J* = 8.9 Hz, ArH), 5.62 (d, 1H, *J* = 4.7 Hz, H3), 5.20 (d, 1H, *J* = 4.5 Hz, H4), 5.04 (m, 1H, *J* = 7.0 Hz, =CH), 4.79 (m, 2H, $=CH_2$), 4.01 (m, 2H, OCH_2), 3.87 (s, 3H, NMe), 3.82 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 209.6, 164.1 (CO), 156.1, 137.0, 130.8,

129.1 (Ar, CH), 127.3, 121.8 (Ar, CH), 119.6 (Ar, CH), 118.9 (Ar, CH), 118.7 (Ar, 2CH), 114.1 (Ar, 2CH), 109.5 (Ar, CH), 106.4, 86.7 (=CH), 82.1 (CH, H3), 75.5 ($=CH_2$), 68.5 (OCH_2), 55.4 (CH, H4), 55.3 (OMe), 33.0 (NMe); IR ($CHCl_3$): ν = 2922, 1744 (CO), 1512, 1246, 832, 745 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{23}N_2O_3[M+H]^+$: 375.1709; found: 375.1712.

β-Lactam-Tethered Allene 37b. From 370 mg (0.84 mmol) of the corresponding β-lactam-tethered alkyne, and after flash chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **37b** (273 mg, 71%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.72 (d, 1H, *J* = 1.5 Hz, ArH), 7.57 (d, 2H, *J* = 9.1 Hz, ArH), 7.30 (dd, 1H, *J* =8.8, 1.7 Hz, ArH), 7.17 (t, 1H, *J* = 8.8 Hz, ArH), 6.96 (s, 1H, ArH), 6.87 (d, 2H, *J* = 9.1 Hz, ArH), 5.44 (m, 1H, =CH), 5.40 (d, 1H, *J* = 5.4 Hz, H3), 5.06 (d, 1H, *J* = 5.0 Hz, H4), 4.93 (m, 2H, $=CH_2$), 4.14 (m, 2H, OCH_2), 3.79 (s, 3H, NMe), 3.74 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 195.1, 164.3 (CO), 157.0, 142.3, 137.4, 130.6 (Ar, CH), 125.0 (Ar, CH), 121.9 (Ar, CH), 121.4, 121.1 (Ar, 2CH), 119.9, 114.2 (Ar, 2CH), 111.0 (Ar, CH), 106.8, 86.7 (=CH), 82.1 (CH, H3), 75.7 ($=CH_2$), 68.9 (OCH_2), 55.4 (CH, H4), 54.9 (OMe), 33.1 (NMe); IR ($CHCl_3$): ν = 2922, 1744 (CO), 1512, 1246, 1082, 797, 752 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{22}BrN_2O_3$ [*M* +H]$^+$: 453.0814; found: 453.0813.

β-Lactam-Tethered Allene 37c. From 275 mg (0.63 mmol) of the corresponding β-lactam-tethered alkyne, and after flash chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **37c** (161 mg, 61%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.06 (d, 1H, *J* = 7.9 Hz, ArH), 7.64 (d, 1H, *J* = 8.0 Hz, ArH), 7.41 (d, 2H, *J* = 8.9 Hz, ArH), 7.32 (t, 1H, *J* = 8.0 Hz, ArH), 7.13 (s, 1H, ArH), 6.85 (d, 2H, *J* = 8.9 Hz, ArH), 5.99 (d, 1H, *J* = 4.8 Hz, H3), 5.08 (d, 1H, *J* = 4.9 Hz, H4), 4.98 (m, 1H, *J* = 6.9 Hz, =CH), 4.63 (m, 2H, $=CH_2$), 4.01 (m, 2H, OCH_2), 3.79 (s, 3H, NMe), 3.78 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 209.4, 164.8 (CO), 156.2, 142.1, 139.8, 133.1 (Ar, CH), 130.8, 120.6 (Ar, CH), 119.4, 118.8 (Ar, 2CH), 118.3 (Ar, CH), 116.3 (Ar, CH), 114.4 (Ar, 2CH), 107.7, 87.0 (=CH), 83.5 (CH, H3), 75.6 ($=CH_2$), 69.1 (OCH_2), 57.2 (CH, H4), 55.5 (OMe), 33.5 (NMe); IR ($CHCl_3$): ν = 2924, 1738 (CO), 1513, 1252, 1031, 800, 741 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{21}N_3O_5$ [*M* +H]$^+$: 420.1559; found: 420.1572.

β-Lactam-Tethered Allene 37d. From 110 mg (0.28 mmol) of the corresponding β-lactam-tethered alkyne, and after flash chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **37d** (62 mg, 55%, mixture of isomers = 75:25) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.62 (d, 0.5H, *J* = 9.0 Hz, ArH), 7.60 (d, 1.5H, *J* = 9.0 Hz, ArH), 7.27 (d, 0.25H, *J* = 2.3 Hz, ArH), 7.23 (d, 0.75H, *J* = 2.3 Hz, ArH), 7.04 (dd, 1H, *J* = 8.9, 2.4 Hz, ArH), 6.81 (d, 0.25H, *J* = 8.9 Hz, ArH), 6.86 (d, 0.75H, *J* = 8.9 Hz, ArH), 6.67 (s, 0.25H, ArH), 6.59 (d, 0.5H, *J* = 9.0 Hz, ArH), 6.56 (d, 1.5H, *J* = 9.0 Hz, ArH), 6.30 (s, 0.75H, ArH), 5.25 (m, 1H, *J* = 6.8 Hz, =CH), 5.08 (d, 0.75H, *J* = 1.7 Hz, H3), 4.95 (d, 0.25H, *J* = 4.7 Hz, H3), 4.87 (d, 0.75H, *J* = 1.7 Hz, H4), 4.69 (d, 0.25H, *J* = 4.7 Hz, H4), 4.51 (m, 0.5H, $=CH_2$), 4.40 (m, 1.5H, $=CH_2$), 4.20 (m, 2H, OCH_2), 3.64 (s, 0.75H, OMe), 3.52 (s, 2.25H, OMe), 3.16 (s, 0.75H, OMe), 3.14 (s, 2.25H, OMe), 2.79 (s, 0.75H, NMe), 2.75 (s, 2.25H, NMe); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 209.8, 164.1 (CO), 156.6, 155.3, 132.9, 132.1, 128.5 (Ar, CH), 127.7 (Ar, CH), 119.0 (Ar, 2CH), 114.6 (Ar, 2CH), 113.3 (Ar,CH), 110.9 (Ar, CH), 110.1, 100.6, 90.0 (=CH), 88.0 (CH, H3), 75.8 ($=CH_2$), 68.9 (OCH_2), 58.1 (CH, H4), 55.4 (OMe), 54.9 (OMe), 32.1 (NMe); IR ($CHCl_3$): ν = 2937, 1740 (CO), 1515, 1278, 1036, 812, 738 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{24}NaN_2O_4[M+Na]^+$: 427.1634; found: 427.1620.

β-Lactam-Tethered Allene 37e. From 110 mg (0.29 mmol) of the corresponding β-lactam-tethered alkyne, and after flash chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **37e** (59 mg, 54%, mixture of isomers = 60:40) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.62 (d, 1.2H, *J* = 9.0 Hz, ArH), 7.58 (d,

0.8H, *J* = 8.6, 3.5 Hz, ArH), 7.13 (t, 0.6H, *J* = 7.8 Hz, ArH), 6.99 (t, 0.4H, *J* = 7.6 Hz, ArH), 6.88 (d, 1.2H, *J* =7.1 Hz, ArH), 6.83 (d, 0.8H, *J* = 7.0 Hz, ArH), 6.60 (d, 1.2H, *J* = 8.9 Hz, ArH), 6.59 (d, 0.8H, *J* = 8.9 Hz, ArH), 6.55 (s, 0.6H, ArH), 6.24 (s, 0.4H, ArH), 5.25 (m, 0.4H, *J* = 6.8 Hz, =CH), 5.09 (d, 0.4H, *J* = 1.6 Hz, H3), 5.02 (d, 0.6H, *J* = 4.7 Hz, H3), 4.92 (m, 0.6H, *J* = 6.9 Hz, =CH), 4.84 (d, 0.4H, *J* = 1.8 Hz, H4), 4.67 (d, 0.4H, *J* = 4.7 Hz, H4), 4.44 (m, 1.2H, $=CH_2$), 4.20 (m, 2H, OCH_2), 3.79 (m, 0.6H, $=CH_2$), 3.16 (s, 1.8H, OMe), 3.13 (s, 1.2H, OMe), 3.02 (s, 1.8H, NMe), 2.97 (s, 1.2H, OMe), 2.27 (s, 3H, Me); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 209.6, 164.2 (CO), 156.5, 131.9, 130.7, 128.3 (Ar, CH), 128.3, 124.8 (Ar, CH), 121.8, 120.3, 119.0 (Ar, 2CH), 116.9 (Ar, CH), 114.6 (Ar, 2CH), 106.7 (Ar, CH), 87.6 (=CH), 83.0 (CH, H3), 75.5 ($=CH_2$), 68.7 (OCH_2), 57.9 (CH, H4), 55.0 (OMe), 36.7 (NMe), 19.5 (Me); IR ($CHCl_3$): ν = 2939, 1742 (CO), 1507, 1260, 1042, 801, 742 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{24}NaN_2O_3[M+Na]^+$: 411.1685; found: 411.1664.

β-Lactam-Tethered Allene 37f. From 130 mg (0.32 mmol) of the corresponding β-lactam-tethered alkyne, and after flash chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **37f** (62 mg, 55%, mixture of isomers = 55:45) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.84 (dd, 0.45H, *J* = 8.2 Hz, ArH), 7.77 (dd, 0.55H, *J* = 8.6 Hz, ArH), 7.74 (d, 1.1H, *J* = 8.2 Hz, ArH), 7.71 (d, 0.9H, *J* = 8.9 Hz, ArH), 7.25 (dd, 0.45H, *J* = 8.2, 1.3 Hz, ArH), 7.09 (dd, 0.55H, *J* = 8.3, 1.3 Hz, ArH), 7.06 (s, 0.45H, ArH), 7.04 (s, 0.55H, ArH), 6.81 (s, 0.45H, ArH), 6.68 d, 1.1H, *J* = 9.3 Hz, ArH), 6.65 (d, 0.9H, *J* = 9.2 Hz, ArH), 6.46 (s, 0.55H, ArH), 5.38 (m, 0.45H, *J* = 6.9 Hz, =CH), 5.21 (d, 0.55H, *J* = 1.7 Hz, H3), 5.15 (d, 0.45H, *J* = 4.8 Hz, H3), 5.02 (m, 0.55H, *J* = 6.8 Hz, =CH), 4.98 (d, 0.55H, *J* = 1.7 Hz, H4), 4.82 (d, 0.45H, *J* = 4.7 Hz, H4), 4.56 (m, 2H, $=CH_2$), 4.32 (m, 1.1H, OCH_2), 3.90 (m, 0.9H, OCH_2), 3.27 (s, 1.35H, OMe), 3.25 (s, 1.65H, OMe), 3.03 (m, 1H, CH), 2.99 (s, 1.35H, NMe), 2.97 (s, 1.65H, NMe), 1.42 (dd, 2.7H, *J* = 6.9, 1.3 Hz, Me), 1.39 (dd, 3.3H, *J* = 6.9, 1.7 Hz, Me); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 209.8 (0.55C), 209.7 (0.45C), 164.2 (0.55CO), 164.1 (0.45CO), 156.5 (0.55C), 156.4 (0.45C), 143.7 (0.55C), 143.1 (0.45C), 138.1 (0.55C), 137.8 (0.45C), 132.1 (0.55C), 132.0 (0.45C), 128.8 (Ar, 0.55CH), 126.9 (Ar, 0.45CH), 119.8 (Ar, 0.55CH), 119.4 (Ar, 0.45CH), 118.9 (Ar, 2CH), 114.6 (Ar, 2CH), 107.5 (Ar, 0.55CH), 107.1 (Ar, 0.45CH), 89.9 (0.55CH, H3), 88.0 (0.55=CH), 87.6 (0.45=CH), 83.1 (0.45CH, H3), 75.8 ($0.55=CH_2$), 75.5 ($0.45=CH_2$), 68.8 ($0.55OCH_2$), 68.6 ($0.45OCH_2$), 58.3 (0.55CH, H4), 55.4 (0.45CH, H4), 54.9 (0.55OMe), 54.8 (0.45OMe), 35.0 (NMe), 32.0 (CH), 24.8 (2Me); IR ($CHCl_3$): ν = 2935, 1740 (CO), 1512, 1258, 1043, 807, 736 cm^{-1}; HRMS (ES): calcd for $C_{26}H_{29}N_2O_3[M+H]^+$: 417.2178; found: 417.2163.

β-Lactam-Tethered Allene 37g. From 382 mg (1.23 mmol) of the corresponding β-lactam-tethered alkyne, and after flash chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **37g** (274 mg, 68%) as a colorless solid; mp 93–94 °C;^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.33 (d, 2H, *J* = 9.1 Hz, ArH), 6.82 (d, 2H, *J* = 9.1 Hz, ArH), 6.33 (d, 1H, *J* = 3.2 Hz, ArH), 5.98 (dd, 1H, *J* = 3.1, 0.9 Hz, ArH), 5.15 (d, 1H, *J* = 4.5 Hz, H3), 5.08 (m, 1H, *J* = 7.0 Hz, =CH), 4.99 (d, 1H, *J* = 4.5 Hz, H4), 4.78 (m, 2H, $=CH_2$), 4.04 (m, 2H, OCH_2), 3.77 (s, 3H, OMe), 2.30 (d, 3H, *J* = 0.7 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 209.8, 163.5 (CO), 156.4, 152.9, 145.8, 130.7, 118.7 (Ar, 2CH), 114.3 (Ar, 2CH), 111.3 (Ar, CH), 106.9 (Ar, CH), 86.8 (=CH), 82.4 (CH, H3), 75.7 ($=CH_2$), 69.0 (OCH_2), 55.9 (CH, H4), 55.4 (OMe), 13.6 (Me); IR ($CHCl_3$): ν = 2919, 1755 (CO), 1512, 1247, 1022, 829, 752 cm^{-1}; HRMS (ES): calcd for $C_{19}H_{20}NO_4[M+H]^+$: 326.1392; found: 326.1389.

β-Lactam-Tethered Allene 37h. From 372 mg (1.2 mmol) of the corresponding β-lactam-tethered alkyne, and after flash chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **37h** (287 mg, 74%) as a colorless solid; mp 105–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.34 (m, 1H, ArH), 7.32 (d, 2H, *J* = 9.0 Hz,

ArH), 7.19 (d, 1H, *J* = 2.9 Hz, ArH), 7.04 (dd, 1H, *J* = 5.1, 3.6 Hz, ArH), 6.80 (d, 2H, *J* = 9.1 Hz, ArH), 5.45 (d, 1H, *J* = 4.5 Hz, H3), 5.03 (d, 1H, *J* = 4.5 Hz, H4), 5.02 (m, 1H, *J* = 6.7 Hz, =CH), 4.76 (m, 2H, $=CH_2$), 3.97 (m, 2H, OCH_2), 3.75 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 209.7, 163.4 (CO), 156.5, 136.8, 130.4, 127.7 (Ar, CH), 126.9 (Ar, CH), 126.7 (Ar, CH), 118.8 (Ar, 2CH), 114.3 (Ar, 2CH), 86.7 (=CH), 82.5 (CH, H3), 75.8 ($=CH_2$), 68.9 (OCH_2), 58.1 (CH, H4), 55.4 (OMe); IR ($CHCl_3$): ν = 2930, 1749 (CO), 1511, 1246, 1116, 830, 708 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{18}NO_3S[M+H]^+$: 328.1007; found: 328.0996.

β-Lactam-Tethered Allene 37i. From 51 mg (0.11 mmol) of the corresponding β-lactam-tethered alkyne, and after flash chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **37i** (32 mg, 60%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.70 (d, 1H, *J* = 8.3 Hz, ArH), 7.53 (t, 2H, *J* = 71 Hz, ArH), 7.40 (m, 3H, ArH), 7.27 (d, 2H, *J* = 8.9 Hz, ArH), 7.26 (m, 1H, ArH), 6.81 (m, 1H, ArH), 6.77 (d, 2H, *J* = 9.0 Hz, ArH), 5.46 (d, 1H, *J* = 4.7 Hz, H3), 5.16 (d, 1H, *J* = 4.7 Hz, H4), 5.11 (m, 1H, *J* = 6.7 Hz, =CH), 4.72 (m, 2H, $=CH_2$), 4.10 (m, 2H, OCH_2), 3.72 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 209.8, 163.7 (CO), 156.4, 153.1, 150.6, 130.6, 130.3, 130.1, 129.0 (Ar, 2CH), 128.6 (Ar, 2CH), 128.2 (Ar, CH), 127.7 (Ar, CH), 126.4 (Ar, 2CH), 123.9 (Ar, 2CH), 118.6 (Ar, 2CH), 117.6, 114.3 (Ar, 2CH), 107.5, 86.7 (=CH), 82.1 (CH, H3), 75.8 ($=CH_2$), 68.9 (OCH_2), 55.4 (CH, H4), 54.9 (OMe); IR ($CHCl_3$): ν = 2926, 1754 (CO), 1512, 1248, 1118, 831, 695 cm^{-1}; HRMS (ES): calcd for $C_{30}H_{26}NO_4$ $[M+H]^+$: 464.1862; found: 464.1849.

β-Lactam-Tethered Allene 37j.From 169 mg (0.48 mmol) of the corresponding β-lactam-tethered alkyne, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **37j** (133 mg, 77%) as a colorless solid; mp 87–88 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.54 (d, 1H, *J* = 7.7 Hz, ArH), 7.51 (d, 1H, *J* = 8.5 Hz, ArH), 7.36 (d, 2H, *J* = 9.2 Hz, ArH), 7.28 (m, 2H, ArH), 6.80 (m, 1H, ArH), 6.81 (d, 2H, *J* = 8.9 Hz, ArH), 5.35 (d, 1H, *J* = 4.7 Hz, H3), 5.13 (d, 1H, *J* = 4.7 Hz, H4), 5.04 (m, 1H, *J* = 6.7 Hz, =CH), 4.68 (m, 2H, $=CH_2$), 4.06 (m, 2H, OCH_2), 3.75 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 209.8, 163.3 (CO), 156.6, 155.1, 150.7, 130.4, 128.1, 124.5 (Ar, CH), 123.0 (Ar, CH), 121.2 (Ar, CH), 118.6 (Ar, 2CH), 114.4 (Ar, 2CH), 111.4 (Ar, CH), 107.0 (Ar, CH), 86.6 (=CH), 82.7 (CH, H3), 75.6 ($=CH_2$), 69.3 (OCH_2), 56.2 (CH, H4), 55.4 (OMe); IR ($CHCl_3$): ν = 2932, 1755 (CO), 1512, 1250, 1115, 830, 750 cm^{-1}; HRMS (ES): calcd for $C_{22}H_{20}NO_4$ $[M+H]^+$: 362.1392; found: 362.1392.

β-Lactam-Tethered Allene 37k. From 424 mg (1.1 mmol) of the corresponding β-lactam-tethered alkyne, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **37k** (304 mg, 69%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.25 (d, 2H, *J* = 8.9 Hz, ArH), 6.77 (d, 2H, *J* = 9.0 Hz, ArH), 6.16 (d, 1H, *J* = 2.0 Hz, ArH), 6.07 (d, 1H, *J* = 2.0 Hz, ArH), 5.69 (d, 1H, *J* = 5.0 Hz, H3), 4.94 (d, 1H, *J* = 5.0 Hz, H4), 4.88 (m, 1H, *J* = 7.1 Hz, =CH), 4.71 (m, 2H, $=CH_2$), 4.02 (m, 1H, OC*H*H), 3.89 (s, 3H, OMe), 3.87 (m, 1H, OCH*H*), 3.80 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.62 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 209.6, 164.9 (CO), 162.1, 161.4, 159.8, 155.6, 131.8, 118.0 (Ar, 2CH), 114.1 (Ar, 2CH), 101.5, 91.6 (Ar, CH), 90.6 (Ar, CH), 87.1 (=CH), 81.7 (CH, H3), 75.3 ($=CH_2$), 69.2 (OCH_2), 56.2 (CH, H4), 55.9 (OMe), 55.4 (OMe), 55.2 (OMe), 54.0 (OMe); IR ($CHCl_3$): ν = 2939, 1749 (CO), 1513, 1122, 829, 750 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{26}NO_6[M+H]^+$: 412.1760; found: 412.1763.

β-Lactam-Tethered Allene 37l. From 264 mg (0.79 mmol) of the corresponding β-lactam-tethered alkyne, and after flash chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **37l** (204 mg, 74%) as a colorless solid; mp 106–107 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.44 (m, 2H, ArH), 7.42 (d, 2H, *J* = 8.9 Hz,

ArH), 7.32 (m, 3H, ArH), 6.87 (d, 2H, *J* = 16.1 Hz, =CH), 6.83 (d, 2H, *J* = 8.9 Hz, ArH), 6.36 (dd, 1H, *J* = 15.9, 8.8 Hz, =CH), 5.26 (m, 1H, *J* = 6.9 Hz, =CH), 4.95 (d, 1H, *J* = 4.7 Hz, H3), 4.78 (m, 2H, $=CH_2$), 4.77 (d, 1H, *J* = 4.4 Hz, H4), 4.20 (m, 2H, OCH_2), 3.77 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 209.8, 163.6 (CO), 156.3, 136.4, 135.9 (=CH), 131.2, 128.7 (Ar, 2CH), 128.4 (=CH), 126.8 (Ar, 2CH), 123.9 (Ar, CH), 118.7 (Ar, 2CH), 114.3 (Ar, 2CH), 86.9 (=CH), 82.4 (CH, H3), 75.9 ($=CH_2$), 69.0 (OCH_2), 61.1 (CH, H4), 55.4 (OMe); IR ($CHCl_3$): ν = 2912, 1742 (CO), 1511, 1244, 1118, 833, 753 cm^{-1}; HRMS (ES): calcd for $C_{22}H_{22}NO_3$ [*M* +H]$^+$: 348.1600; found: 348.1596.

β-Lactam-Tethered Allene 37m. From 250 mg (0.69 mmol) of the corresponding β-lactam-tethered alkyne, and after flash chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **37m** (200 mg, 77%) as a colorless solid; mp 98–99 ºC; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.42 (d, 2H, *J* = 9.1 Hz, ArH), 7.38 (d, 2H, *J* = 8.8 Hz, ArH), 6.87 (d, 2H, *J* = 8.9 Hz, ArH), 6.83 (d, 2H, *J* = 9.1 Hz, ArH), 6.80 (d, 1H, *J* = 16.3 Hz, =CH), 6.20 (dd, 1H, *J* = 15.9, 8.9 Hz, =CH), 5.26 (m, 1H, *J* = 6.7 Hz, =CH), 4.93 (d, 1H, *J* = 4.7 Hz, H3), 4.77 (d, 1H, *J* = 4.5 Hz, H4), 4.76 (m, 2H, $=CH_2$), 4.20 (m, 2H, OCH_2), 3.82 (s, 3H, OMe), 3.76 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 209.8, 163.7 (CO), 159.8, 156.3, 135.9 (=CH), 131.2, 128.7, 128.1 (Ar, 2CH), 121.4 (=CH), 118.7 (Ar, 2CH), 114.3 (Ar, 2CH), 114.0 (Ar, 2CH), 87.0 (=CH), 82.4 (CH, H3), 75.9 ($=CH_2$), 69.0 (OCH_2), 61.3 (CH, H4), 55.4 (OMe), 55.3 (OMe); IR ($CHCl_3$): ν = 2912, 1743 (CO), 1511, 1246, 1118, 832, 750 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{24}NO_4$ [*M* +H]$^+$: 378.1705; found: 378.1711.

β-Lactam-Tethered Allene 37n. From 68 mg (0.16 mmol) of the corresponding β-lactam-tethered alkyne (mixture of isomers = 75:25), and after flash chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **37n** [(26 mg, 38%,mixture of isomers = 75:25) + (23 mg, 33%,isomerically pure)]. **β-Lactam-Tethered Allene 37n (d.r. = 75:25)**:Colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.07 (dd, 0.75H, *J* = 7.9, 0.7 Hz, ArH), 8.06 (dd, 0.25H, *J* = 7.9, 0.8 Hz, ArH), 7.64 (dd, 0.75H, *J* = 8.2, 0.7 Hz, ArH), 7.63 (dd, 0.25H, *J* = 8.2, 0.7 Hz, ArH), 7.44 (m, 0.5H, ArH), 7.43 (d, 1.5H, *J* = 9.1 Hz, ArH), 7.32 (t, 0.75H, *J* = 8.0 Hz, ArH), 7.31 (t, 0.25H, *J* = 8.0 Hz, ArH), 7.15 (s, 0.75H, ArH), 7.11 (s, 0.25H, ArH), 6.86 (m, 0.5H, ArH), 6.85 (d, 1.5H, *J* = 9.0 Hz, ArH), 6.02 (dd, 0.25H, *J* = 5.1, 0.8 Hz, H3), 5.99 (dd, 0.75H, *J* = 4.8, 0.6 Hz, H3), 5.14 (d, 1H, *J* = 5.0 Hz, H4), 5.11 (m, 1H, =CH), 4.76 (m, 1.5H, $=CH_2$), 4.60 (m, 05H, $=CH_2$), 4.18 (m, 0.25H, OCH), 3.91 (m, 0.75H, OCH), 3.79 (s, 3H, NMe), 3.78 (s, 3H, OMe), 1.15 (d, 0.75H, *J* = 6.3 Hz, Me), 0.80 (d, 2.25H, *J* = 6.3 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 208.5, 165.0 (CO), 156.1, 139.8, 133.2, 130.9, 120.5 (Ar, CH), 118.8 (Ar, 2CH), 118.3 (Ar, CH), 116.2 (Ar, CH), 114.4 (Ar, 2CH), 107.9, 92.2 (=CH), 82.4 (CH, H3), 76.3 ($=CH_2$), 75.1 (OCH), 57.2 (CH, H4), 55.4 (OMe), 33.5 (NMe), 21.0 (Me); IR ($CHCl_3$): ν = 2916, 1740 (CO), 1514, 1240, 1112, 832, 752 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{24}N_3O_5$[*M* +H]$^+$: 434.1716; found: 434.1711.**β-Lactam-Tethered Allene 37n (isomerically pure)**: Colorless solid; mp 110–111 ºC; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.06 (dd, 1H, *J* = 7.9, 0.6 Hz, ArH), 7.63 (d, 1H, *J* = 8.1, 0.7 Hz, ArH), 7.44 (d, 2H, *J* = 9.1 Hz, ArH), 7.31 (t, 1H, *J* = 8.0 Hz, ArH), 7.11 (s, 1H, ArH), 6.86 (d, 2H, *J* = 9.19 Hz, ArH), 6.03 (d, 1H, *J* = 4.7 Hz, H3), 5.08 (d, 1H, *J* = 5.1 Hz, H4), 4.64 (m, 1H, =CH), 4.58 (m, 2H, $=CH_2$), 4.18 (m, 1H, OCH), 3.79 (s, 3H, NMe), 3.78 (s, 3H, OMe), 1.16 (d, 3H, *J* = 6.3 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 208.0, 165.5 (CO), 156.1, 139.8, 133.0, 131.0, 120.5 (Ar, CH), 118.8 (Ar, 2CH), 118.2 (Ar, CH), 116.2 (Ar, CH), 114.4 (Ar, 2CH), 108.2, 92.3 (=CH), 82.5 (CH, H3), 76.2 ($=CH_2$), 75.1 (OCH), 57.2 (CH, H4), 55.5 (OMe), 33.5 (NMe), 20.7 (Me); IR ($CHCl_3$): ν = 2915, 1740 (CO), 1515, 1243, 1110, 832, 753 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{24}N_3O_5$ [*M* +H]$^+$: 434.1716; found: 434.1711.

β-Lactam-Tethered Allene 37o. From 101 mg (0.31 mmol) of the corresponding β-lactam-tethered alkyne (mixture of isomers = 70:30), and after flash chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **37o** (58 mg, 55%, mixture of isomers = 70:30) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.33 (d, 1.4H, *J* = 8.9 Hz, ArH), 7.32 (d, 0.6H, *J* = 8.9 Hz, ArH), 6.82 (d, 2H, *J* = 9.0 Hz, ArH), 6.32 (d, 1H, *J* = 3.0 Hz, ArH), 5.97 (d, 1H, *J* = 1.8 Hz, ArH), 5.13 (m, 1H, H3), 5.11 (m, 0.7H, H4), 5.09 (m, 1H, =CH), 5.01 (d, 0.3H, *J* = 4.7 Hz, H4), 4.82 (m, 1.4H, $=CH_2$), 4.72 (m, 0.6H, $=CH_2$), 4.19 (m, 0.3H, OCH), 3.80 (m, 0.7H, OCH), 3.76 (s, 3H, OMe), 2.30 (s, 3H, Me), 1.26 (d, 0.9H, *J* = 6.3 Hz, Me), 1.08 (d, 2.1H, *J* = 6.3 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 208.9 (M), 208.4 (m), 163.8 (CO, m), 163.4 (CO, M), 156.3, 152.8 (M), 152.6 (m), 146.0 (M + m), 130.8 (M + m), 118.61 (Ar, 2C, M), 118.59 (Ar, 2C, m), 114.2 (Ar, 2CH), 111.3 (Ar, CH, M), 111.1 (Ar, CH, m), 106.8 (Ar, CH), 92.3 (=CH, m), 91.6 (=CH, M), 81.7 (H3, m), 80.6 (H3, M), 76.10 ($=CH_2$, m), 76.06 ($=CH_2$, M), 76.0 (OCH, m), 74.5 (OCH, M), 56.6 (H4, m), 55.9 (H4, M), 55.4 (OMe, M + m), 21.1 (Me, m), 20.8 (Me, M), 13.6 (Me, M + m); IR ($CHCl_3$): ν = 2915, 1756 (CO), 1510, 1244, 1025, 826, 752 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{22}NO_4$[*M* +H]$^+$: 340.1549; found: 340.1542.

Bis(β-Lactam)-Tethered Bis(Allene) 37p. From 110 mg (0.21 mmol) of the corresponding bis(β-lactam)-tethered bis(alkyne)(mixture of isomers = 80:20), and after flash chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **37p** (62 mg, 53%, mixture of isomers = 80:20) as a colorless solid; mp 112–113ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.30 (d, 3.2H, *J* = 9.2 Hz, ArH), 7.20 (d, 0.8H, *J* = 9.2 Hz, ArH), 6.80 (d, 3.2H, *J* = 9.1 Hz, ArH), 6.71 (d, 0.8H, *J* = 9.0 Hz, ArH), 6.52 (s, 0.4H, ArH), 6.49 (s, 1.6H, ArH), 5.20 (d, 1.6H, *J* = 4.5 Hz, H3), 5.19 (d, 0.4H, *J* = 4.4 Hz, H3), 5.02 (m, 0.4H, =CH), 4.91 (d, 2H, *J* = 4.7 Hz, H4), 4.91 (m, 1.6H, *J* = 7.0 Hz, =CH), 4.79 (m, 0.8H, $=CH_2$), 4.74 (m, 3.2H, $=CH_2$), 4.03 (m, 0.8H, OCH_2), 3.89 (m, 3.2H, OCH_2), 3.75 (s, 4.8H, OMe), 3.74 (s, 1.2H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 209.7 (2C, M + m), 163.3 (2CO, M + m), 156.5 (2C, M), 156.4 (2C, m), 148.6 (2C, M + m), 130.4 (2C, M + m), 118.5 (4C, Ar, CH, M), 118.4 (4C, Ar, CH, m), 114.3 (4C, Ar, CH, M + m), 112.0 (2C, Ar, CH, m), 111.7 (2C, Ar, CH, M), 86.7 (2C, =CH, m), 86.6 (2C, =CH, M), 82.3 (2C, CH3, M + m), 76.0 (2C, $=CH_2$, M), 75.9 (2C, $=CH_2$, m), 69.2 (2C, OCH_2, M), 69.0 (2C, OCH_2, m), 55.6 (2C, CH4, M + m), 55.4 (2C, OMe, m), 55.3 (2C, OMe, M); IR ($CHCl_3$): ν = 2925, 1750 (CO), 1511, 1253, 1020, 832, 751 cm^{-1}; HRMS (ES): calcd for $C_{32}H_{31}N_2O_7$[*M* +H]$^+$: 555.2131; found: 555.2136.

(Vinyloxy)buta-1,2-diene 39h. From 65 mg (0.40 mmol) of alkyne **F**, and after flash chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **39h** (44 mg, 62%) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ^{o}C): δ = 7.01 (d, 1H, *J* = 3.5 Hz, Ar), 6.92 (d, 1H, *J* = 5.1 Hz, Ar), 6.82 (dd, 1H, *J* = 5.1, 3.4 Hz, Ar), 5.84 (d, 1H, *J* = 6.4 Hz, =CH), 5.58 (d, 1H, *J* = 6.5 Hz, =CH), 5.06 (qu, 1H, *J* = 6.7 Hz, =CH), 4.51 (dt, 2H, *J* = 6.6, 2.5 Hz, $=CH_2$), 3.99 (dt, 2H, *J* = 6.9, 2.5 Hz, OCH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ^{o}C): δ = 209.5, 143.6 (=CH), 138.8, 126.5 (Ar, CH), 125.2 (Ar, CH), 124.4 (Ar, CH), 101.7 (=CH), 87.7 (=CH), 76.3 ($=CH_2$), 70.4 (OCH_2); IR ($CHCl_3$): ν = 2940, 1650, 1359, 695, 666 cm^{-1}; HRMS (ES): calcd for $C_{10}H_{11}OS$[*M*]$^+$: 179.0531; found: 179.0520.

General Procedure for the Gold-Catalyzed Rearrangement Reaction of β-Lactam-Tethered Allenes1. Preparation of Cage Adducts 38a–p. The appropriate allene **37** (0.10 mmol) was added to a stirred solution of [AuClIPr] (0.005 mmol) and $AgSbF_6$ (0.005 mmol) in 1,2-dichloroethane (1.3 m) under argon. The resulting mixture was stirred under argon atmosphere at the appropriate temperature until disappearance of the starting material (TLC). After filtration through a pad of Celite, the mixture was extracted with ethyl acetate (3 x 3 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure.

Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure cage adducts **38**.

Cage Adduct 38a. From 30 mg (0.08 mmol) of the β-lactam-tethered allene **37a**, and after flash chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound **38a** (15 mg, 83%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.67 (d, 1H, *J* = 7.9 Hz, ArH), 7.29 (d, 1H, *J* = 8.5 Hz, ArH), 7.22 (t, 1H, *J* = 6.9 Hz, ArH), 7.10 (td, 1H, *J* = 7.9, 1.2 Hz, ArH), 6.99 (s, 1H, ArH), 4.21 (d, 1H, *J* = 1.5 Hz, OCH), 4.12 (t, 1H, *J* = 3.9 Hz, OCH), 3.76 (s, 3H, NMe), 3.19 (s, 1H, CH), 1.77 (d, 1H, *J* = 10.6 Hz, C*H*H), 1.57 (d, 1H, *J* = 10.6 Hz, CH*H*), 1.51 (m, 1H, CH), 1.46 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 136.7, 127.6, 126.6 (Ar, CH), 121.3 (Ar, CH), 118.7 (Ar, CH), 118.5 (Ar, CH), 112.5, 109.2 (Ar, CH), 73.7 (OCH), 51.4 (OCH), 40.0 (CH), 33.2 (CH_2), 32.7 (NMe), 16.0 (CH), 11.7 (CH); IR ($CHCl_3$): ν = 2936, 1685, 1475, 1062, 795, 741 cm^{-1}; HRMS (ES): calcd for $C_{15}H_{16}NO[M+H]^+$: 226.1232; found: 226.1226.

Cage Adduct 38b. From 99 mg (0.22 mmol) of the β-lactam-tethered allene **37b**, and after flash chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave compound **38b** (43 mg, 64%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.73 (d, 1H, *J* = 1.5 Hz, ArH), 7.28 (dd, 1H, *J* = 8.6, 1.7 Hz, ArH), 7.15 (d, 1H, *J* = 8.6 Hz, ArH), 6.99 (s, 1H, ArH), 4.18 (d, 1H, *J* = 1.9 Hz, OCH), 4.11 (t, 1H, *J* = 4.0 Hz, OCH), 3.73 (s, 3H, NMe), 3.10 (s, 1H, CH), 1.76 (d, 1H, *J* = 10.6 Hz, C*H*H), 1.53 (d, 1H, *J* = 10.8 Hz, C*H*H), 1.49 (m, 2H, 2CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 135.4, 129.2, 127.8 (Ar, CH), 124.1 (Ar, CH), 121.1 (Ar, CH), 112.3, 112.0, 110.7 (Ar, CH), 73.6 (OCH), 51.3 (OCH), 39.9 (CH), 33.2 (CH_2), 32.8 (NMe), 15.9 (CH), 11.7 (CH); IR ($CHCl_3$): ν = 2935, 1717, 1475, 1059, 792 cm^{-1}; HRMS (ES): calcd for $C_{15}H_{15}BrNO[M+H]^+$: 304.0337; found: 304.0336.

Cage Adduct 38c. From 35 mg (0.08 mmol) of the β-lactam-tethered allene **37c**, and after flash chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **38c** (19 mg, 85%) as a colorless solid; mp 107–108 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.86 (d, 1H, *J* = 7.9 Hz, ArH), 7.50 (d, 1H, *J* = 8.0 Hz, ArH), 7.25 (m, 2H, ArH), 4.18 (d, 1H, *J* = 1.6 Hz, OCH), 4.13 (t, 1H, *J* = 3.6 Hz, OCH), 3.84 (s, 3H, NMe), 3.44 (s, 1H, ArH), 1.83 (d, 1H, *J* = 10.2 Hz, C*H*H), 1.51 (dt, 1H, *J* = 10.5, 1.9 Hz, CH*H*), 1.47 (t, 2H, *J* = 3.9 Hz, 2CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 143.0, 139.4, 131.9 (Ar, CH), 119.9 (Ar, CH), 119.3, 117.2 (Ar, CH), 115.1 (Ar, CH), 112.2, 74.3 (OCH), 51.7 (OCH), 41.4 (CH), 33.2 (CH_2), 33.0 (NMe), 15.8 (CH), 11.7 (CH); IR ($CHCl_3$): ν = 2923, 1681, 1511, 1345, 750 cm^{-1}; HRMS (ES): calcd for $C_{15}H_{15}N_2O_3[M+H]^+$: 271.1083; found: 271.1060.

Cage Adduct 38d. From 38mg (0.09 mmol) of the β-lactam-tethered allene **1d**, and after flash chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound **2d** (18 mg, 74%) as a colorless solid; mp 100–101 ºC; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.22 (d, 1H, *J* = 2.3 Hz, ArH), 7.12 (dd, 1H, *J* = 8.9, 2.4 Hz, ArH), 6.94 (d, 1H, *J* = 8.6 Hz, ArH), 6.87 (s, 1H, ArH), 4.12 (s, 1H, OCH), 3.90 (t, 1H, *J* = 3.9 Hz, OCH), 3.62 (s, 3H, NMe), 3.03 (s, 1H, CH), 2.97 (s, 3H, OMe), 1.39 (m, 2H, CH_2), 1.26 (t, 1H, *J* = 4.8 Hz, CH), 1.08 (t, 1H, *J* = 4.7 Hz, CH); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 154.6, 132.7, 128.9, 112.5, 111.9 (Ar, CH), 110.3 (Ar, CH), 101.2 (Ar, CH), 74.0 (OCH), 55.6 (OMe), 51.6 (OCH), 40.5 (CH), 33.6 (CH_2), 32.1 (NMe), 17.1 (CH), 12.2 (CH); IR ($CHCl_3$): ν = 2935, 1654, 1461, 1060, 776, 720 cm^{-1}; HRMS (ES): calcd for $C_{16}H_{18}NO_2[M+H]^+$: 256.1338; found: 256.1326.

Cage Adduct 38e. From 33 mg (0.08 mmol) of the β-lactam-tethered allene **37e**, and after flash chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent

gave compound **38e** (12 mg, 57%) as a colorless oil; ^{1}H NMR (300 MHz, acetone-d_6, 25 ^{o}C): δ = 7.39 (dd, 1H, *J* = 7.6, 0.9 Hz, ArH), 6.89 (s, 1H, ArH), 6.83 (m, 2H, ArH), 4.07 (d, 1H, *J* = 1.9 Hz, OCH), 4.02 (t, 1H, *J* = 4.0 Hz, OCH), 4.01 (s, 3H, NMe), 3.09 (s, 1H, CH), 2.71 (s, 3H, Me), 1.73 (d, 1H, *J* = 9.9 Hz, C*H*H), 1.40 (m, 1H, CH*H*), 1.38 (m, 1H, CH), 1.36 (m, 1H, CH); ^{13}C NMR (75 MHz, acetone-d_6, 25 ^{o}C): δ = 136.4, 130.0, 129.4 (Ar, CH), 124.5 (Ar, CH), 121.9, 119.5 (Ar, CH), 117.5 (Ar, CH), 113.1, 74.0 (OCH), 51.8 (OCH), 40.7 (CH), 36.7 (NMe), 33.8 (CH_2), 19.8 (Me), 16.5 (CH), 12.1 (CH); IR ($CHCl_3$): ν = 2940, 1683, 1475, 1054, 790, 732 cm^{-1}; HRMS (ES): calcd for $C_{16}H_{18}NO[M+H]^{+}$: 240.1388; found: 240.1387.

Cage Adduct 38f. From 38 mg (0.09 mmol) of the β-lactam-tethered allene **37f**, and after flash chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound **38f** (14 mg, 60%) as a colorless solid; mp 96–97 ^{o}C; ^{1}H NMR (300 MHz, C_6D_6, 25 ^{o}C): δ = 7.62 (d, 1H, *J* = 8.3 Hz, ArH), 7.17 (m, 1H, ArH), 7.02 (d, 1H, *J* = 0.7 Hz, ArH), 6.84 (s, 1H, ArH), 4.11 (d, 1H, *J* = 1.2 Hz, OCH), 3.90 (t, 1H, *J* = 3.8 Hz, OCH), 3.06 (m, 1H, CH), 3.04 (s, 1H, CH), 3.02 (s, 3H, NMe), 1.40 (d, 6H, *J* = 7.0 Hz, 2Me), 1.36 (m, 2H, CH_2), 1.25 (t, 1H, *J* = 4.7 Hz, CH), 1.07 (t, 1H, *J* = 4.7 Hz, CH); ^{13}C NMR (75 MHz, C_6D_6, 25 ^{o}C): δ = 142.6, 137.7, 127.1, 126.5 (Ar, CH), 119.0 (Ar, CH), 118.3 (Ar, CH), 112.9, 106.7 (Ar, CH), 74.0 (OCH), 51.6 (OCH), 40.6 (CH), 35.1 (NMe), 33.6 (CH_2), 31.9 (CH), 25.0 ($2CH_3$), 17.0 (CH), 12.2 (CH); IR ($CHCl_3$): ν = 2935, 1676, 1475, 1078, 792, 737 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{22}NO[M+H]^{+}$: 268.1701; found: 268.1709.

Cage Adduct 38g. From 50 mg (0.15 mmol) of the β-lactam-tethered allene **37g**, and after flash chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent gave compound **38g** (17 mg, 65%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 5.98 (d, 1H, *J* = 2.9 Hz, ArH), 5.87 (dd, 1H, *J* = 2.9, 0.9 Hz, ArH), 4.25 (d, 1H, *J* = 2.0 Hz, OCH), 4.07 (t, 1H, *J* = 4.0 Hz, OCH), 2.89 (s, 1H, CH), 2.26 (s, 3H, Me), 1.64 (dd, 1H, *J* = 10.5, 0.9 Hz, C*H*H), 1.48 (d, 1H, *J* = 10.4 Hz, CH*H*), 1.46 (m, 1H, CH), 1.45 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 152.2, 150.4, 106.6 (Ar, CH), 106.0 (Ar, CH), 72.7 (OCH), 51.2 (OCH), 42.8 (CH), 32.9 (CH_2), 14.4 (CH), 13.5 (Me), 11.3 (CH); IR ($CHCl_3$): ν = 2927, 1712, 1513, 1250, 927, 799, 755 cm^{-1}; HRMS (ES): calcd for $C_{11}H_{13}O_2$ [*M* +H]$^{+}$: 177.0916; found: 177.0904.

Cage Adduct 38h. From 50 mg (0.15 mmol) of the β-lactam-tethered allene **37h**, and after flash chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent gave compound **38h** (18 mg, 68%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.17 (dd, 1H, *J* = 5.1, 1.3 Hz, ArH), 6.94 (dd, 1H, *J* = 5.0, 3.4 Hz, ArH), 6.90 (d, 1H, *J* = 3.4 Hz, ArH), 4.16 (m, 1H, OCH), 4.15 (t, 1H, *J* = 4.1 Hz, OCH), 3.21 (s, 1H, CH), 1.71 (d, 1H, *J* = 10.5 Hz, C*H*H), 1.55 (m, 1H, CH*H*), 1.51 (m, 1H, CH), 1.49 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 142.9, 126.2 (Ar, CH), 124.3 (Ar, CH), 123.9 (Ar, CH), 74.8 (OCH), 51.6 (OCH), 44.7 (CH), 33.3 (CH_2), 17.9 (CH), 12.5 (CH); IR ($CHCl_3$): ν = 2920, 1717, 1510, 1200, 927, 796, 750 cm^{-1}; HRMS (ES): calcd for $C_{10}H_{11}OS[M+H]^{+}$: 179.0531; found: 179.0518.

Cage Adduct 38i. From 75 mg (0.16 mmol) of the β-lactam-tethered allene **37i**, and after flash chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave compound **38i** (23 mg, 45%) as a colorless solid; mp 103–104 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.73 (dd, 2H, *J* = 8.5, 1.3 Hz, ArH), 7.67 (dd, 2H, *J* = 8.5, 1.4 Hz, ArH), 7.42 (m, 4H, ArH), 7.29 (m, 2H, ArH), 6.87 (s, 1H, ArH), 4.28 (d, 1H, *J* = 1.9 Hz, OCH), 4.20 (t, 1H, *J* = 3.8 Hz, OCH), 3.13 (s, 1H, CH), 1.75 (d, 1H, *J* = 10.6 Hz, C*H*H), 1.56 (m, 1H, CH*H*), 1.53 (m, 1H, CH), 1.52 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ= 152.1, 148.5, 131.5, 130.8, 128.6 (4C, Ar, CH), 127.1 (2C, Ar, CH), 126.0 (2C, Ar, CH), 123.7 (2C, Ar, CH), 122.1 108.4 (Ar, CH), 74.4 (OCH), 51.8 (OCH), 40.3 (CH), 33.5 (CH_2),

16.6 (CH), 11.8 (CH); IR ($CHCl_3$): ν = 2930, 1715, 1513, 1265, 996, 795 cm^{-1}; HRMS (ES): calcd for $C_{22}H_{19}O_2$ [*M* +H]$^+$: 315.1385; found: 315.1374.

Cage Adduct 38j. From 60 mg (0.17 mmol) of the β-lactam-tethered allene **37j**, and after flash chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent gave compound **38j** (19 mg, 35%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.48 (dd, 1H, *J* = 6.7, 0.9 Hz, ArH), 7.41 (d, 1H, *J* = 7.9 Hz, ArH), 7.19 (m, 2H, ArH), 6.52 (s, 1H, ArH), 4.40 (d, 1H, *J* = 2.0 Hz, OCH), 4.16(t, 1H, *J* = 3.7 Hz, OCH), 3.08 (s, 1H, CH), 1.74 (d, 1H, *J* = 10.4 Hz, C*H*H), 1.63 (m, 1H, CH*H*), 1.53 (m, 2H, 2CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 157.2, 154.5, 128.8, 123.3 (Ar, CH), 122.4 (Ar, CH), 120.5 (Ar, CH), 110.7 (Ar, CH), 103.1 (Ar, CH), 72.6 (OCH), 51.4 (OCH), 43.2 (CH), 33.2 (CH_2), 14.6 (CH), 11.5 (CH); IR ($CHCl_3$): ν = 2934, 1723, 1483, 1060, 797 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{13}O_2$ [*M* +H]$^+$: 213.0916; found: 213.0913.

Cage Adduct 38k.From 101 mg (0.24 mmol) of the β-lactam-tethered allene **37k**, and after flash chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave compound **38k** (20 mg, 32%) as a colorless solid; mp 96–97 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 6.12 (s, 2H, ArH), 4.30 (br s, 1H, OCH), 3.99 (t, 1H, *J* = 3.9 Hz, OCH), 3.79 (s, 9H, 3OMe), 3.01 (s, 1H, CH), 1.62 (d, 1H, *J* = 9.5 Hz, C*H*H), 1.34 (m, 1H, CH*H*), 1.32 (m, 2H, 2CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 160.0, 159.4, 123.3, 119.0, 91.5 (2C, Ar, CH), 74.6 (OCH), 55.9 (2OMe), 55.3 (OMe), 53.2 (OCH), 42.2 (CH), 31.2 (CH_2), 15.0 (CH), 11.9 (CH); IR ($CHCl_3$): ν = 2936, 1712, 1476, 1057, 795, 754 cm^{-1}; HRMS (ES): calcd for $C_{15}H_{19}O_4$[*M* +H]$^+$: 263.1283; found: 263.1288.

Cage Adduct 38l. From 63 mg (0.18 mmol) of the β-lactam-tethered allene **37l**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave compound **38l** (13 mg, 37%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.36 (d, 2H, *J* = 8.0 Hz, ArH), 7.30 (d, 2H, *J* = 7.1 Hz, ArH), 7.20 (t, 1H, *J* = 7.3 Hz, ArH), 6.47 (d, 1H, *J* = 16.1 Hz, =CH), 6.09 (d, 1H, *J* = 16.1, 8.5 Hz, =CH), 4.07 (m, 1H, OCH), 4.05 (t, 1H, *J* = 3.8 Hz, OCH), 2.48 (d, 1H, *J* = 8.5 Hz, CH), 1.59 (d, 1H, *J* = 10.6 Hz, C*H*H), 1.44 (m, 1H, CH*H*), 1.37 (m, 2H, 2CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 137.4, 130.7 (=CH), 128.8 (=CH), 128.4 (2C, Ar, CH), 127.0 (Ar, CH), 126.1 (Ar, 2CH), 73.9 (OCH), 51.2 (OCH), 47.5 (CH), 32.9 (CH_2), 15.6 (CH), 11.4 (CH); IR ($CHCl_3$): ν = 2934, 1710, 1475, 1060, 794 cm^{-1}; HRMS (ES): calcd for $C_{14}H_{15}O$[*M* +H]$^+$: 199 1123; found: 199.1119.

Cage Adduct 38m. From 81 mg (0.22 mmol) of the β-lactam-tethered allene **37m**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave compound **38m** (16 mg, 32%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.29 (d, 2H, *J* = 8.8 Hz, ArH), 6.84 (d, 2H, *J* = 8.8 Hz, ArH), 6.42 (d, 1H, *J* = 16.1 Hz, =CH), 5.94 (d, 1H, *J* = 15.9, 8.5 Hz, =CH), 4.05 (m, 1H, OCH), 4.04 (t, 1H, *J* = 4.1 Hz, OCH), 3.81 (s, 3H, OMe), 2.45 (d, 1H, *J* = 8.5 Hz, CH), 1.57 (d, 1H, *J* = 10.4 Hz, C*H*H), 1.41 (d, 1H, *J* = 10.6 Hz, CH*H*), 1.37 (t, 1H, *J* = 4.4 Hz, CH), 1.28 (t, 1H, *J* = 4.4 Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 158.8, 130.3, 130.0 (=CH), 127.2 (2C, Ar, CH), 126.5 (=CH), 113.9 (2C, Ar, CH), 74.0 (OCH), 55.3 (OMe), 51.2 (OCH), 47.4 (CH), 32.9 (CH_2), 15.6 (CH), 11.4 (CH); IR ($CHCl_3$): ν = 2934, 1711, 1479, 1062, 798, 750 cm^{-1}; HRMS (ES): calcd for $C_{15}H_{17}O_2$[*M* +H]$^+$: 229.1229; found: 229.1221.

Cage Adduct 38n. From 27 mg (0.06 mmol) of the β-lactam-tethered allene **37n**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave compound **38n** (12 mg, 68%) as a colorless solid; mp 108–109 ºC; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.72 (dd, 1H, *J* = 7.9, 0.9 Hz, ArH), 7.45 (dd, 1H, *J* = 8.2, 0.9 Hz, ArH), 7.12 (m, 2H, ArH), 4.00 (d, 1H, *J* = 1.6 Hz, OCH), 3.72 (s, 3H, NMe), 3.36 (s, 1H, CH), 1.73 (d, 1H, *J* = 10.7 Hz, C*H*H), 1.66 (s. 3H, Me), 1.55 (dt, 1H, *J* = 10.6, 2.0 Hz, CH*H*),

1.18 (m, 2H, 2CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 142.8, 139.5, 132.0 (Ar, CH), 120.0 (Ar, CH), 119.7, 117.2 (Ar, CH), 115.2 (Ar, CH), 112.2, 73.6 (OCH), 58.8, 43.3 (CH), 34.4 (CH_2), 33.3 (NMe), 21.4 (CH), 17.5 (CH), 14.3 (Me); IR ($CHCl_3$): ν = 2925, 1690, 1510, 1342, 751 cm^{-1}; HRMS (ES): calcd for $C_{16}H_{17}N_2O_3$ [*M* +H]$^+$: 285.1239; found: 285.1227.

Cage Adduct 38o. From 26 mg (0.08 mmol) of the β-lactam-tethered allene **37o**, and after flash chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent gave compound **38o** (7 mg, 42%) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ^{o}C): δ = 6.20 (d, 1H, *J* = 3.0 Hz, ArH), 5.97 (d, 1H, *J* = 2.9 Hz, ArH), 4.20 (d, 1H, *J* = 1.5 Hz, OCH), 2.92 (s, 1H, CH), 2.20 (d, 3H, *J* = 0.4 Hz Me), 1.66 (s, 3H, Me), 1.49 (dt, 1H, *J* = 10.5, 1.7 Hz, C*H*H), 1.33 (d, 1H, *J* = 10.3 Hz, CH*H*), 1.17 (d, 1H, *J* = 5.5 Hz, CH), 0.98 (t, 1H, *J* = 5.5 Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 152.2, 150.4, 106.7 (Ar, CH), 106.1 (Ar, CH), 74.6 (OCH), 58.6, 44.5 (CH), 34.4 (CH_2), 20.0 (Me), 17.1 (CH), 14.0 (CH), 13.5 (Me); IR ($CHCl_3$): ν = 2928, 1714, 1510, 1250, 921, 795, 757 cm^{-1}; HRMS (ES): calcd for $C_{12}H_{15}O_2$ [*M* +H]$^+$: 191.1072; found: 191.1063.

Bis(Cage)Adduct 38p. From 47 mg (0.09 mmol) of the bis(β-lactam)-tethered bis(allene) **37p**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave compound **38p** (8 mg, 36%) as a colorless solid; mp 109–110 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 6.01 (s, 2H, ArH), 4.25 (s, 2H, 2OCH), 4.07 (t, 2H, *J* = 3.8 Hz, 2OCH), 2.89 (s, 2H, 2CH), 1.64 (d, 2H, *J* = 10.7 Hz, 2C*H*H), 1.48 (m, 2H, 2CH*H*), 1.45 (m, 2H, 2CH), 1.42 (m, 2H, 2CH); ^{13}C NMR (175 MHz, $CDCl_3$, 25 ^{o}C): δ = 152.4 (2C), 106.7 (Ar, CH), 106.5 (Ar, CH), 72.7 (OCH), 72.6 (OCH), 51.3 (OCH), 51.2 (OCH), 42.8 (2C, CH), 33.0 (CH_2), 32.9 (CH_2), 14.6 (CH), 14.4 (CH), 11.4 (CH), 11.3 (CH); IR ($CHCl_3$): ν = 2930, 1708, 1515, 946, 790 cm^{-1}; HRMS (ES): calcd for $C_{16}H_{17}O_3$[*M* +H]$^+$: 257.1178; found: 257.1173.

Computational Details: All the calculations reported in this paper were obtained with the GAUSSIAN 09 suite of programs.[13] Electron correlation was partially taken into account using the hybrid functional usually denoted as B3LYP[14] in conjunction with the D3 dispersion correction suggested by Grimme et al.[15] using the standard double-ζ quality plus polarization def2-SVP basis set[16] for all atoms. Solvents effects were taken into account by means of the Polarizable Continuum Model (PCM)[17] using dichloroethane as solvent during the geometry optimizations. Reactants and products were characterized by frequency calculations,[18] and have positive definite Hessian matrices. Transition structures (TS's) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the Intrinsic Reaction Coordinate (IRC) method.[19] Single point calculations were performed to estimate the change in the Gibbs energies at the B3LYP-D3 level using the triple-ζ quality plus polarization def2-TZVP basis set for all atoms. This level is denoted PCM(dichloroethane)-B3LYP-D3/def2-TZVP//PCM(dichloroethane)-B3LYP-D3/def2-SVP.

VII.4. Notes and references

1 For representative reviews, see: (a) D. Pflästerer and A. S. K. Hashmi, *Chem. Soc. Rev.,* 2016, **45**, 1331; (b) L. Fensterbank and M. Malacria, *Acc. Chem. Res.,* 2014, **47**, 953; (c) B.-L. Lu, L. Dai and M. Shi, *Chem. Soc. Rev.,* 2012, **41**, 3318; (d) A. Corma, A. Leyva-Pérez and M. J. Sabater, *Chem. Rev.,* 2011, **111**, 1657; (e) A. S. K. Hashmi and G. J. Hutchings, *Angew. Chem. Int. Ed.,* 2006, **45**, 7896.

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5 Under otherwise identical conditions, the N1 phenyl analogue of allenyl-β-lactam **37a** provided adduct **38a** in a diminished 27% yield.

6 CCDC-960487 contains the supplementary crystallographic data for this paper.

7 Two related oxatricycloheptanes has been prepared through gold(I)-catalyzed cycloisomerization of 1,6-enynes: (a) C. Ferrer, M. Raducan, C. Nevado, C. K. Claverie, A. M. Echavarren, *Tetrahedron*, 2007, **63**, 6306. Polycyclic hetero-cage compounds have attracted synthetic chemists because of their unusual shapes, symmetries, and chemically distinct surfaces: (b) H.-J. Wu in *Advances in Strained and Interesting Organic Molecules Supplement 1: Carbocyclic and Heterocyclic Cage Compounds and Their Building Blocks*, ed. K. K. Laali, JAI Press, Stamford, CT, 1999, p. 167.

8 The retro-[2+2] alkene–isocyanate cycloaddition may occur thermally, but high activation energies have been calculated: (a) J. E. Rode and J. C. Dobrowolski, *J. Phys. Chem. A,* 2006, **110**, 3723; (b) F. P. Cossío, G. Roa, B. Lecea and J. M. Ugalde, *J. Am. Chem. Soc.,* 1995, **117**, 12306; (c) L. A. Paquette, M. J. Wyvratt Jr. and G. R. Allen, *J. Am. Chem. Soc.,* 1970, **92**, 1763. For a mechanistic insight of the osmium-catalysed β-lactam fragmentation, see: (d) L. Casarrubios, M. A. Esteruelas, C. Larramona, A. Lledós, J. G. Muntaner, E. Oñate and M. A. Ortuño, M A. Sierra, *Chem. Eur. J.,* 2015, **21**, 16781. However, taking the acidity of the β-lactam H4 into account, a mechanistic scenario that involves a sequential N1–C4 β-lactam bond cleavage promoted by SbF_6^-, followed by thermal decarboxylation cannot be completely ruled out.

9 For studies of the gold-catalyzed allene-diene isomerization, see: (a) J.-M. Chen, C.-J. Chang, Y.-J. Ke and R.-S. Liu, *J. Org. Chem.,* 2014, **79**, 4306; (b) A. Basak, K. Chakrabarty, A. Ghosh and G. K. Das, *J. Org. Chem.,* 2013, **78**, 9715.

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11 Highly stable β-lactam precursors **37** are readily prepared in good overall yields beginning from the appropriate imine by Staudinger reaction with acetoxyacetyl chloride in the presence of Et_3N, followed by sequential transesterification, treatment with propargyl bromide, and final Crabbé reaction. (Vinyloxy)buta-1,2-dienes **39** are relatively unstable precursors. Besides, their preparation required nine steps from propargyl alcohol, while just a four-step sequence is needed for the preparation of β-lactam allenes **37**. In addition, the aryl moiety in β-lactam precursors **37** came from aldehydes while for the introduction of the arene functionality in enol ethers **39** a less available boronic acid is required. The atom-efficiency for the gold-catalyzed reaction is higher starting from alkenes **39**. However, taking into account that for the preparation of (vinyloxy)buta-1,2-dienes **39** the incorporation and further cleavage of a TIPS group, a TfO moiety, and a boronic acid $B(OH)_2$ are required, the atom economy of the overall process is in favour of the use of β-lactam allenes.

12 All the calculations reported herein were performed at the PCM(dichloroethane)-B3LYP-D3/def2-TZVP //PCM(dichloroethane)-B3LYP-D3/def2-SVP level. See Computational Details in the Supplementary Information.

13 Gaussian 09, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, Jr. J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

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VIII. CAPÍTULO 5

VIII.1. Acid-Catalyzed Synthesis of α,β-Disubstituted Conjugated Enones by a Meyer–Schuster-Type Rearrangement in Allenols

A novel, direct and simple methodology to gain access to α,β-disubstituted conjugated enones from α-allenols in a sustainable metal catalysis context, considering the inexpensiveness and environmentally friendliness of iron(III) species and protons, has been developed.

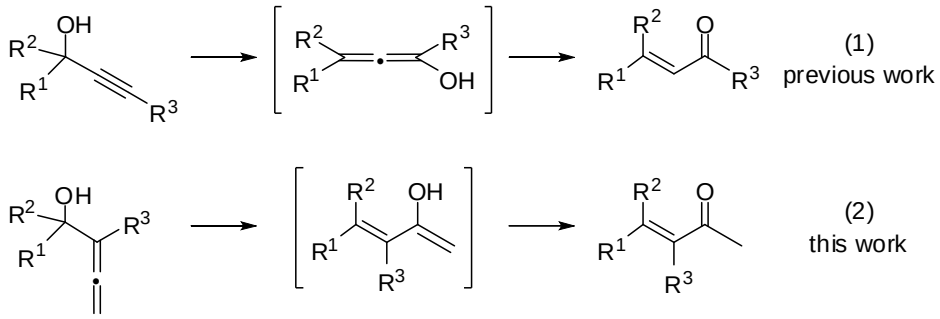
Adv. Synth. Catal. **2015**, *357*, 1070

VIII.2. Communication

The use of α,β-unsaturated ketones as starting materials to prepare a variety of compounds, as well as the presence of this structural unit in a large number of biologically active natural products have led to increased recent interest in methods of preparing such compounds.[1] Classical methods such as aldol condensation and olefination strategies present serious drawbacks. Thus, harsh conditions and modest yields are usually encountered in the aldol condensation, while the generation of noxius waste by-products coupled with low atom economy are disadvantages of Wittig-type reactions. Besides, these traditional protocols usually require strong basic conditions, which may be incompatible with selectivity control as well as sensitive functional groups. An alternative method of synthesis of α,β-unsaturated ketones is the Meyer–Schuster rearrangement carbon [Scheme VIII.1, Eq. (1)], which starts from propargylic alcohols and consists in a formal 1,3-hydroxy shift followed by tautomerization.[2]

In this regard, the rearrangement of allenic alcohols may be a possible solution to produce α,β-unsaturated ketones with high reaction efficiency; although this achievement has not yet been fully accomplished.[3] Besides, the allenol rearrangement could provide competitive advantages, because in contrast with the alkynol rearrangement, the allenic version could afford internally substituted conjugated enones.

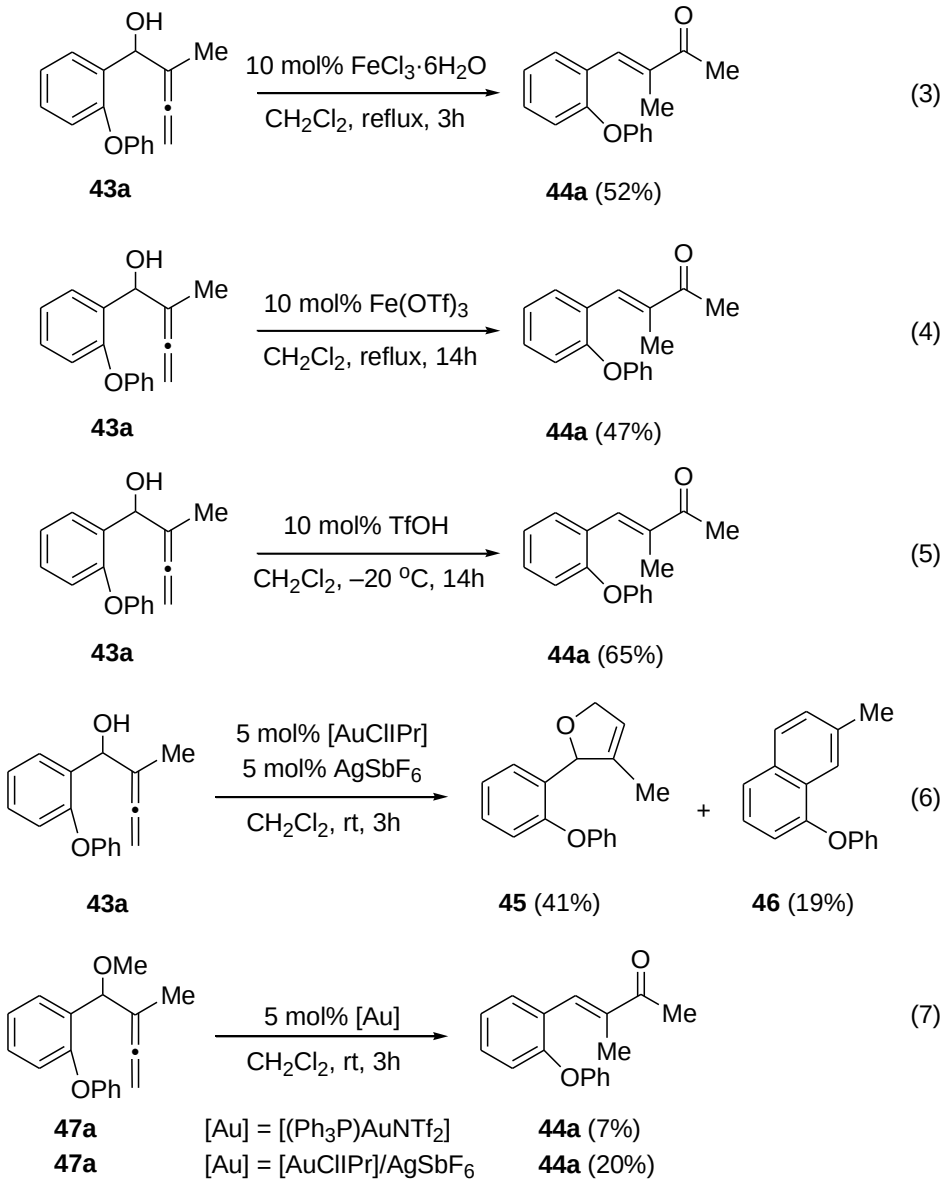
On the other hand, iron-catalyzed processes have attracted recent attention because iron is one of the most inexpensive and environmentally benign metals on earth.[4] Following up on our combined interest in the area of allenes and metals,[5] and considering the economic attractiveness and the environmentally friendliness of iron species we chose to study the iron-catalyzed reaction of α-allenols as a sustainable metal-catalyzed route to access α,β-disubstituted conjugated enones carbon [Scheme VIII.1, Eq. (2)].



Scheme VIII.1. Alkynol *versus* allenol isomerization.

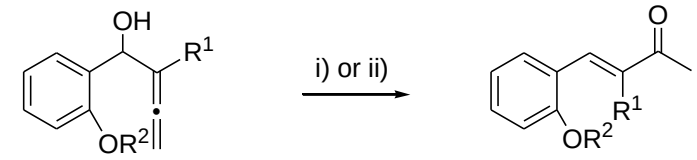
Starting allenols **43** were readily prepared in good overall yield from the appropriate carbaldehyde through a regioselective indium-mediated Barbier-type carbonyl–allenylation reaction in aqueous media using our methodology.[6] Initially, we were attempting the iron-catalyzed cycloisomerization reaction of allenol **43a**. Unexpectedly, the alkenone **44a** was obtained using either iron(III) chloride hexahydrate or iron(III) triflate. Considering the abundance and non-toxicity of iron(III) species, we became interested in developing an allenol-based Meyer–Schuster rearrangement methodology for the preparation of functionalized α,β-unsaturated ketones. The reaction was next optimized by screening solvent and temperature. A 52% yield of α,β-unsaturated ketone **44a** was obtained through the use of $FeCl_3 \cdot 6H_2O$ (10 mol%) and dichloromethane as the solvent at 40 °C [Scheme VIII.2, Eq. (3)]. A similar result was encountered through the use of catalytic amounts of $Fe(OTf)_3$ [Scheme VIII.2, Eq. (4)]. This reaction could also be catalyzed by $Bi(OTf)_3$ and $In(OTf)_3$, but with diminished effectiveness. Different Lewis acid catalysts such as $InCl_3$, $ZnCl_2$, and AgOTf were found to be completely ineffective in carrying out any reorganization of the allenol. A Brønsted acid such as the super acid TfOH was shown to efficiently transform **43a** into **44a** at low temperature [Scheme VIII.2, Eq. (5)]. To check whether gold complexes are good catalysts for this rearrangement, reaction of allenol **43a** in presence of $[(Ph_3P)AuNTf_2]$ was also carried out.[7] The reaction does take a different course, with a separable mixture of oxycyclization and carbocyclization adducts **45** and **46** being obtained [Scheme VIII.2, Eq. (6)].[8] It was interesting at this point to test the reactivity of a protected allenol moiety under gold-catalyzed conditions. When the hydroxyl functionality in **43a** was protected in the form of methyl ether as in **47a**, the

gold-catalyzed Meyer–Schuster type rearrangement occurred,[9] but in low yield [Scheme VIII.2, Eq. (7)].



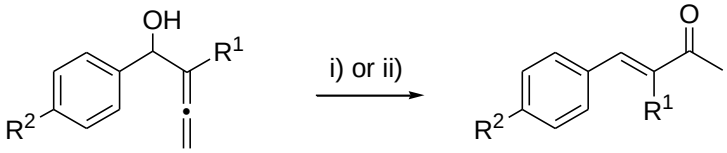
Scheme VIII.2. Divergent metal-catalyzed rearrangement of allenol derivatives **43a** and **47a**.

With optimized conditions in hand, we then examined the generality of this acid-catalyzed rearrangement protocol in α-allenols **43**. When allenols **43c–43e**, **43g**, and **43i** were tested as precursors using triflic acid catalysis, it furnished the corresponding reorganization products **44c–44e**, **44g**, and **44i** (Scheme VIII.3).



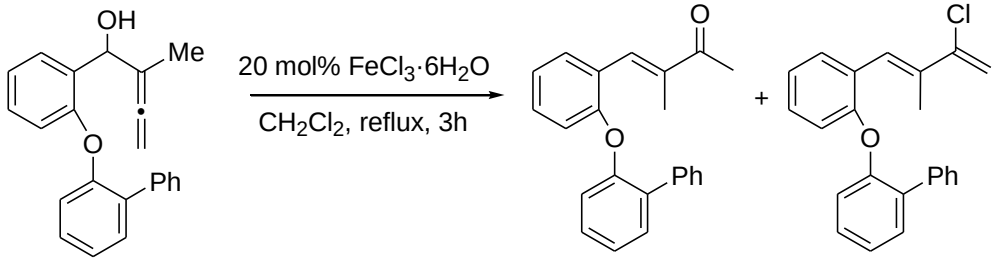
43b R^1 = Ph, R^2 = Ph
43c R^1 = Me, R^2 = 4-BrC_6H_4
43d R^1 = Me, R^2 = 2-PhC_6H_4

44b (51%, method ii)
44c (61%, method i)
44d (62%, method i)



43e R^1 = Me, R^2 = Cl
43f R^1 = Ph, R^2 = Cl
43g R^1 = Me, R^2 = MeO
43h R^1 = Ph, R^2 = MeO
43i R^1 = Me, R^2 = Me
43j R^1 = Ph, R^2 = Me
43k R^1 = Ph, R^2 = H

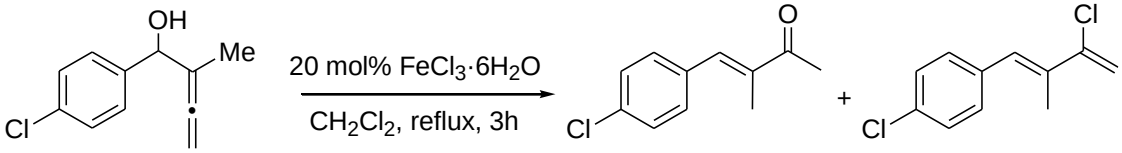
44e (70%, method i)
44f (55%, method ii)
44g (65%, method i)
44h (52%, method ii)
44i (61%, method i)
44j (51%, method ii)
44k (50%, method ii)



43d

44d (22%)

48d (46%)



43e

44e (19%)

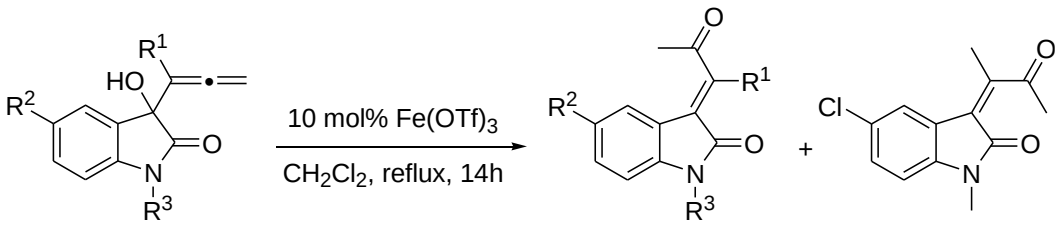
48e (30%)

Scheme VIII.3. Acid-catalyzed rearrangement of allenols **43**. *Reagents and conditions:* i) 10 mol% TfOH, CH_2Cl_2, –20 °C, 14 h. ii) 10 mol% $Fe(OTf)_3$, CH_2Cl_2, reflux, 14 h.

Complete conversion was observed for phenyl-substituted allenes **43b**, **43f**, **43h**, **43j**, and **43k** but complicated reaction mixtures were obtained. Competing reactions lead to the exclusion of the above allenols as efficient substrates for the TfOH-promoted reaction. Fortunately, $Fe(OTf)_3$ did afford the corresponding α,β-

unsaturated ketones **44b**, **44f**, **44h**, **44j**, and **44k** in fair yields (Scheme VIII.3). The reactions were selective and only Meyer–Schuster adducts were formed, with no trace of isomeric oxycyclization products. Electron-withdrawing and electron-donating substituents on the aryl ring were tolerated with only little influence on the reactivity (Scheme VIII.3). Chlorodienes **48** were often obtained as important component during the $FeCl_3 \cdot 6H_2O$-catalyzed reaction of α-allenols **43** (Scheme VIII.3).

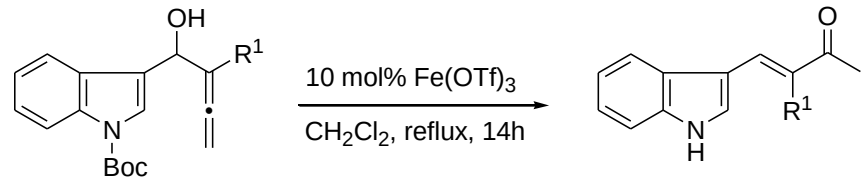
3-Methyleneindolin-2-ones are not only recognized as versatile intermediates in organic synthesis,[10] but also exhibit interesting biological activities.[11] Consequently, the iron-catalyzed stereoselective synthesis of 3-alkenyl-oxindole **50a** from 2-indolinone-tethered allenol **49a** under similar conditions is noteworthy (Scheme VIII.4).



49a R^1 = Ph, R^2 = H, R^3 = Me
49b R^1 = Ph, R^2 = H, R^3 = H
49c R^1 = Ph, R^2 = Cl, R^3 = Me
49d R^1 = Me, R^2 = Cl, R^3 = Me

50a (57%)
50b (64%)
50c (49%)
50d (35%)

51d (12%)



52a R^1 = Ph
52b R^1 = Me

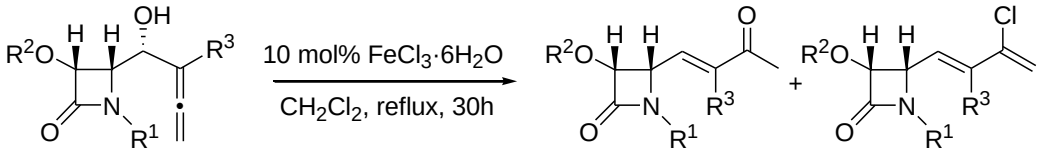
53a (20%)
53b (24%)

Scheme VIII.4. $Fe(OTf)_3$-catalyzed rearrangement of indole-linked allenols **49** and **52**.

Allenic *NH*-indolinone **49b** smoothly provided the 3-alkenyl-oxindole rearranged adduct **50b** as sole product (Scheme VIII.4), becaming apparent that substitution at the nitrogen atom of the heterocycle should had little effect upon the reactivity of the allenol moiety. Allenic 5-chloro-indolinone **49c** smoothly provided the rearranged adduct **50c** in reasonable yield (Scheme VIII.4). The major product

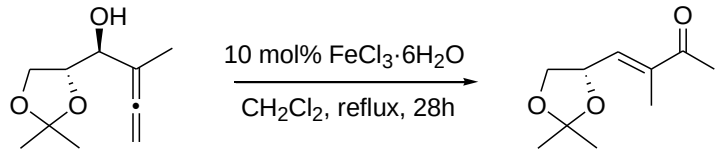
for the methyl-substituted allenol **49d** was assigned to be the *E* form, α,β-unsaturated ketone **50d**, being the unexpected *Z* isomer **51d** the minor component (Scheme VIII.4).[12] The iron-catalyzed rearrangement reaction of (indol-3-yl)-α-allenols **52a** and **52b** afforded N-Boc deprotected α,β-unsaturated ketones **53a** and **53b** in modest yields (Scheme VIII.4).[13]

Unfortunately, enantiopure allenols **54–56** derived from aliphatic aldehydes were not as rewarding as their aromatic counterparts. Neither $Fe(OTf)_3$ nor TfOH reacted well, because decomposition adducts were detected. Interestingly, the use of $FeCl_3{\cdot}6H_2O$ afforded identifiable products. However, this variation led to less efficiency in terms of chemical yields of the ketone derivatives **57** and **59** (Scheme VIII.5).

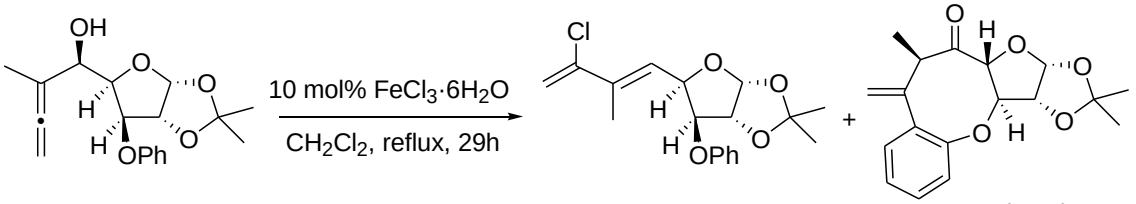


54a R^1 = isobutyl, R^2 = Ph, R^3 = Me
54b R^1 = isobutyl, R^2 = Ph, R^3 = Ph
54c R^1 = Bn, R^2 = Ph, R^3 = Me
54d R^1 = R^2 = 4-$MeOC_6H_4$, R^3 = Me

57a (8%) **58a** (9%)
(*E*)-**58b** (27%)/(*Z*)-**58b** (10%)[a]
57c (20%)
57d (31%)



55 **59** (24%)



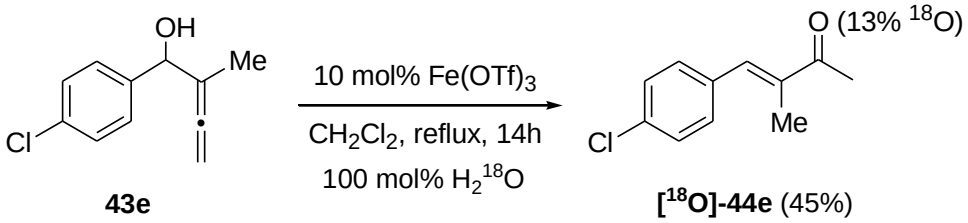
56 **60** (7%) **61** (15%)

Scheme VIII.5. $FeCl_3$-catalyzed rearrangement of allenols **54–56**. [a]The reaction was carried out using 20 mol% $FeCl_3$.

Chlorodienes **58a**, **58b**, and **60** were obtained in appreciable amounts. Surprisingly, tricycle **61** was obtained as major component from allene sugar

derivative **56** (Scheme VIII.5). Importantly, no erosion of the stereochemical integrity was observed in enantiopure products **57–61**.

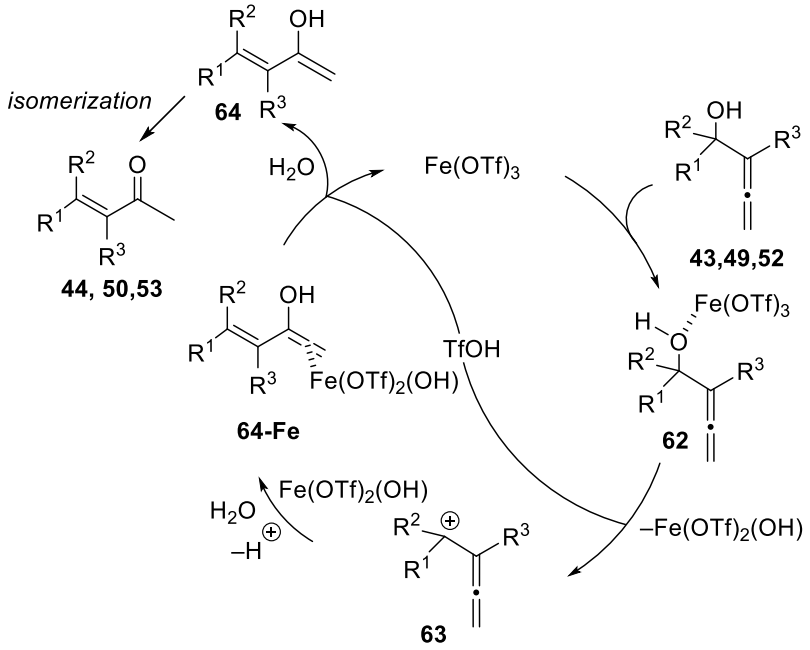
In order to interpret the rearrangement reaction outcome in a more useful manner, an ^{18}O-labeling experiment was planned. ^{18}O-incorporation was monitored as an indicator of a mechanistic scenario that involves an indirect intermolecular 1,3-shift of the OH group. Mass spectrometric analysis of the product of reaction of allenol **43e** under $Fe(OTf)_3$ catalysis in presence of 100 mol% $H_2{}^{18}O$, showed that the α,β-unsaturated ketone **44e** was partially ^{18}O-labelled (Scheme VIII.6), revealing that the carbonylic oxygen atom may arise from external H_2O.



43e **[^{18}O]-44e** (45%)

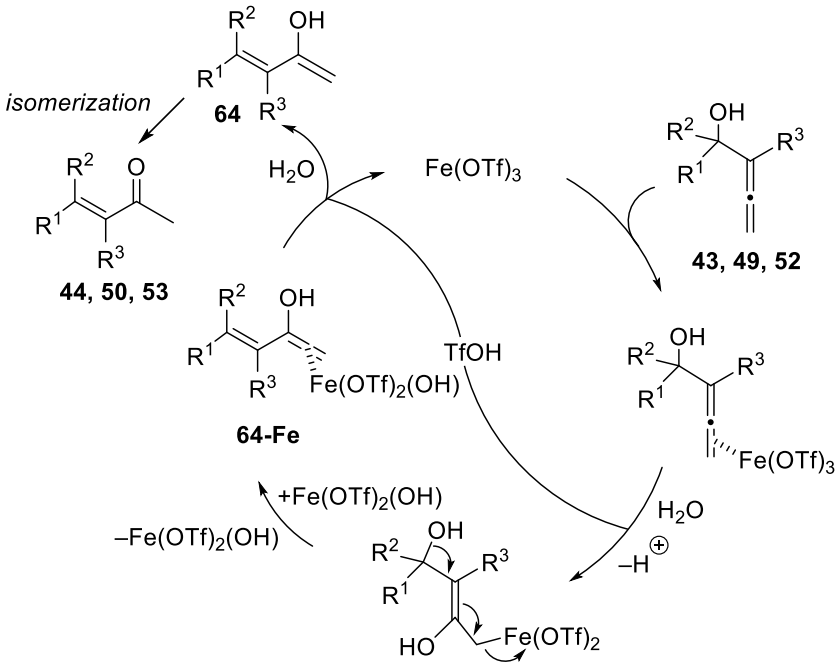
Scheme VIII.6. Labeling experiment.

The high stereoselectivity of the rearrangement which occurs by (*E*)-alkene formation, is independent of the stereochemistry of the starting α-allenol (racemic or enantiopure). This fact and the labelling experiment may indicate a stepwise path with the participation of carbocationic species. A possible reaction pathway leading to α,β-unsaturated ketones from α-allenols was proposed as shown in Scheme VIII.7. $Fe(OTf)_3$ acts as a Lewis acid interacting with the alcohol group in the allenol moiety. Initial σ-coordination of the metal to the hydroxy group of allenols **43**, **49**, and **52**, leads to complexes **62**. Separation of the alcohol group by $Fe(OTf)_3$ generates allenic cation **63**, which would facilitate the nucleophilic addition of water to the carbenium ion, thus leading to a metalated intermediate **64-Fe**. Next, demetalation yields neutral dienol species **64** and regenerates the iron catalyst. Finally, isomerization could generate α,β-unsaturated ketones **44**, **50** and **53** (Scheme VIII.7).



Scheme VIII.7. Mechanistic explanation for the iron-catalyzed rearrangement of allenols through elimination–addition.

However, taking all the experiments into account, an alternative addition–elimination mechanism scenario as sketched in Scheme VIII.8 cannot be completely ruled out.



Scheme VIII.8. Mechanistic explanation for the iron-catalyzed rearrangement of allenols through addition – elimination.

In conclusion, a novel, direct and simple methodology to gain access to α,β-disubstituted conjugated enones from α-allenols in a sustainable metal catalysis context, considering the inexpensiveness and environmentally friendliness of iron(III) species and protons, has been developed.

VIII.3. Experimental Section

General methods: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300 or Bruker AMX-500. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{13}C, 77.0 ppm). Coupling constants "*J*" are expressed in Hertz (multiplicity: s = singulet, d = doublet, dd = double doublet, t = triplet, dt = double triplet, q = quadruplet, quint = quintuplet, sext = sextuplet, sept = septuplet, m =multiplet). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electrospray mode (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. Specific rotation $[\alpha]_D$ is given in 10^{-1} deg cm^2 g^{-1} at 20 °C, and the concentration (*c*) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

Typical Procedure for the TfOH-Catalyzed Rearrangement Reaction of α-Allenols 43. To a cooled solution of the appropriate allenol **43** (1.0 mmol) in dichloromethane (10 mL) at –20 ºC, TfOH (0.10 mmol) was added. The reaction mixture was stirred at –20 ºC until the starting material disappeared as indicated by TLC. Water (1 mL) was added, and the mixture was allowed to warm to room temperature before being partitioned between dichloromethane and water. The organic extract was concentrated under vacuum, and purified by flash column chromatography eluting with ethyl acetate/hexanes mixtures. Spectroscopic and analytical data for pure forms of compounds **44** follow.[14]

α,β-Unsaturated Ketone 44a. From 134 mg (0.53 mmol) of α-allenol **43a**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound **44a** (88 mg, 65%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.66 (s, 1H, =CH), 7.45 (dd, 1H, *J* = 7.7, 1.3 Hz, Ar), 7.34 (t, 2H, *J* = 7.6 Hz, Ar), 7.31 (td, 1H, *J* = 7.4, 1.6 Hz, Ar), 7.18 (t, 1H, *J* = 7.9 Hz, Ar), 7.11 (t, 1H, *J* = 7.4 Hz, Ar), 6.97 (m, 3H, Ar), 2.36 (s, 3H, COMe), 2.01 (t, 3H, *J* = 1.2 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 202.2 (CO), 157.2, 155.0, 138.6, 134.9 (=CH), 130.6 (Ar, CH), 130.0 (Ar, CH), 129.8 (Ar, 2CH), 127.7, 123.3 (Ar, CH), 123.3 (Ar, CH), 119.1 (Ar, CH), 118.1 (Ar, 2CH), 25.7 (Me), 12.3 (Me); IR ($CHCl_3$): ν = 3066, 1668 (CO), 1484, 1238, 753 cm^{-1}; HRMS (ES): calcd for $C_{17}H_{16}O_2$ [*M*]$^+$: 252.1150; found: 252.1142.

α,β-Unsaturated Ketone 44c. From 108 mg (0.33 mmol) of α-allenol **43c**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **44c** (67 mg, 61%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.60 (s, 1H, =CH), 7.44 (m, 1H, Ar), 7.43 (d, 2H, *J* = 9.0 Hz, Ar), 7.34 (td, 1H, *J* = 7.7, 1.7 Hz, Ar), 7.20 (td, 1H, *J* = 7.9, 1.0 Hz, Ar), 6.96 (dd, 1H, *J* = 8.1, 1.1 Hz, Ar), 6.84 (d, 2H, *J* = 9.0 Hz, Ar), 2.37 (s, 3H, COMe), 1.99 (t, 3H, *J* = 1.4 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 198.6 (CO), 159.1, 157.8, 138.9, 134.4 (=CH), 132.8 (Ar, 2CH), 130.8 (Ar, CH), 130.2 (Ar, CH), 128.7, 123.9 (Ar, CH), 119.8 (Ar, 2CH), 119.2 (Ar, CH), 116.4, 25.8 (Me), 13.0 (Me); IR ($CHCl_3$): ν = 3066, 1667 (CO), 1477, 1234, 756 cm^{-1}; HRMS (ES): calcd for $C_{17}H_{15}BrO_2$ [*M*]$^+$: 330.0255; found: 330.0245.

α,β-Unsaturated Ketone 44d. From 238 mg (0.73 mmol) of allenol **43d**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **44d** (147 mg, 62%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.60 (s, 1H, =CH), 7.49 (m, 3H, Ar), 7.32 (m, 4H, Ar), 7.24 (t, 3H, *J* = 7.6 Hz, Ar), 7.07 (t, 1H, *J* = 7.5 Hz, Ar), 6.90 (dd, 1H, *J* = 8.0, 1.2 Hz, Ar), 6.85 (d, 1H, *J* = 7.3 Hz, Ar), 2.36 (s, 3H, COMe), 1.94 (d, 3H, *J* = 1.3 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 200.4 (CO), 155.4, 153.4, 153.2, 137.6, 136.8, 135.2 (Ar, CH), 133.4, 131.4 (Ar, CH), 130.4 (Ar, CH),

129.8 (Ar, CH), 129.1 (Ar, 2CH), 128.7 (Ar, CH), 128.0 (Ar, 2CH), 127.3 (Ar, CH), 124.3 (Ar, CH), 122.5 (Ar, CH), 119.7 (Ar, CH), 117,3 (=CH), 25.7 (Me), 12.9 (Me); IR ($CHCl_3$): ν = 3061, 1666 (CO), 1476, 1223, 745, 695 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{20}O_2$ $[M]^+$: 328.1463; found: 328.1473.

α,β-Unsaturated Ketone 44e. From 340 mg (1.75 mmol) of allenol **43e**, and after chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave compound **44e** (239 mg, 70%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.38 (d, 1H, *J* = 0.9 Hz), 7.32 (d, 2H, *J* = 8.9 Hz), 7.28 (d, 2H, *J* = 8.8 Hz), 2.39 (s, 3H), 1.96 (d, 3H, *J* = 1.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 200.0, 138.1, 134.4, 130.9 (2C), 129.5, 128.8 (2C), 128.7, 25.9, 13.0; IR ($CHCl_3$): ν = 3070, 1668 (CO), 751, 696 cm^{-1}; HRMS (ES): calcd for $C_{11}H_{11}ClO$ $[M]^+$: 194.0498; found: 194.0497.

α,β-Unsaturated Ketone 44g. From 40 mg (0.21 mmol) of α-allenol **43g**, and after chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent gave compound **44g** (26 mg, 65%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.40 (s, 1H), 7.34 (d, 2H, *J* = 8.8 Hz), 6.88 (d, 2H, *J* = 8.9 Hz), 3.78 (s, 3H), 2.38 (s, 3H), 2.00 (d, 3H, *J* = 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 200.3, 139.6, 135.9, 131.6 (2C), 129.8, 128.5, 113.9 (2C), 55.4, 28.5, 12.9; IR ($CHCl_3$): ν = 3069, 1670 (CO), 1481, 1236, 751, 696 cm^{-1}; HRMS (ES): calcd for $C_{12}H_{14}O_2$ $[M]^+$: 190.0994; found: 190.0998.

α,β-Unsaturated Ketone 44i. From 100 mg (0.57 mmol) of α-allenol **43i**, and after chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **44i** (61 mg, 61%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.42 (s, 1H), 7.27 (d, 2H, *J* = 8.0 Hz), 7.15 (d, 2H, *J* = 8.0 Hz), 2.38 (s, 3H), 2.32 (s, 3H), 1.99 (d, 3H, *J* = 1.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 200.0, 140.3, 139.1, 137.2, 133.2, 130.2 (2C), 129.6 (2C), 26.3, 22.0, 13.4; IR ($CHCl_3$): ν = 3074, 1672 (CO), 1482, 1233, 752, 697 cm^{-1}; HRMS (ES): calcd for $C_{12}H_{14}O$ $[M]^+$: 174.1045; found: 174.1047.

Typical Procedure for the $Fe(OTf)_3$-Catalyzed Rearrangement Reaction of α-Allenols 43, 49, and 52. To a solution of the appropriate allenol **43** (1.0 mmol) in dichloromethane (10 mL), $Fe(OTf)_3$ (0.10 mmol) was added. The reaction mixture was stirred at reflux temperature until the starting material disappeared as indicated by TLC. After filtration through a pad of Celite, the mixture was concentrated under vacuum, and purified by flash column chromatography eluting with ethyl acetate/hexanes mixtures. Spectroscopic and analytical data for pure forms of compounds **44**, **50**, **51**, and **53** follow.

α,β-Unsaturated Ketone 44b. From 68 mg (0.22 mmol) of α-allenol **43b**, and after chromatography of the residue using hexanes/ethyl acetate (7:1) as eluent gave compound **44b** (36 mg, 51%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.94 (s, 1H, =CH), 7.37 (m, 6H, Ar), 7.15 (m, 3H, Ar), 7.01 (d, 2H, *J* = 8.6 Hz, Ar), 6.87 (d, 1H, *J* = 8.1 Hz, Ar), 6.76 (d, *J* = 4.1 Hz, Ar), 2.33 (s, 3H, COMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 199.4 (CO), 157.4, 156.1, 156.0, 142.0, 133.6 (=CH), 130.9 (Ar, CH), 130.3 (Ar, CH), 129.9 (Ar, 2CH), 129.8 (Ar, 2CH), 128.7 (Ar, 2CH), 127.8 (Ar, CH), 126.6, 123.4 (Ar, CH), 123.0 (Ar, CH), 118.9 (Ar, CH), 118.6 (Ar, 2CH), 27.4(Me); IR ($CHCl_3$): ν = 3061, 1675 (CO), 1482, 1233, 752, 695 cm^{-1}; HRMS (ES): calcd for $C_{22}H_{18}O_2$ $[M]^+$: 314.1307; found: 314.1306.

α,β-Unsaturated Ketone 44f. From 200 mg (0.78 mmol) of α-allenol **43f**, and after chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave compound **44f** (110 mg, 55%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.59 (s, 1H, =CH), 7.42 (m, 3H, Ar), 7.16 (m, 2H, Ar), 7.14 (d, 2H, *J* = 8.6 Hz, Ar), 6.96 (d, 2H, *J* = 8.5 Hz, Ar), 2.30 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 199.1 (CO), 141.3, 137.2

(=CH), 136.6, 135.1, 133.1, 132.0 (Ar, 2CH), 129.4 (Ar, 2CH), 129.2 (Ar, 2CH), 128.5 (Ar, 2CH), 128.1 (Ar, CH), 28.0 (Me); IR ($CHCl_3$): ν= 2930, 1662 (CO), 1457, 1090, 810 cm^{-1}; HRMS (ES): calcd for $C_{16}H_{13}OCl$ $[M]^+$: 256.0655; found: 256.0659.

α,β-Unsaturated Ketone 44h. From 95 mg (0.38 mmol) of allenol **43h**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound **44h** (49 mg, 52%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.55 (s, 1H), 7.34 (m, 3H), 7.11 (dd, 2H, *J* = 8.0, 1.9 Hz), 6.90 (d, 2H, *J* = 8.9 Hz), 6.61 (d, 2H, *J* = 8.9 Hz), 3.68 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 199.2, 160.5, 138.8, 138.7, 137.5, 132.7 (2C), 129.6 (2C), 129.2 (2C), 128.5, 127.2, 113.8 (2C), 55.2, 27.9; IR ($CHCl_3$): ν = 3075, 1670 (CO), 1471, 1225, 742, 692 cm^{-1}; HRMS (ES): calcd for $C_{17}H_{16}O_2$ $[M]^+$: 252.1150; found: 252.1157.

α,β-Unsaturated Ketone 44j. From 220 mg (0.93 mmol) of α-allenol **43j**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **44j** (112 mg, 51%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.64 (s, 1H, =CH), 7.40 (m, 3H, Ar), 7.19 (dd, 2H, *J* = 7.8, 2.0 Hz, Ar), 6.99 (d, 2H, *J* = 8.3 Hz, Ar), 6.93 (d, 2H, *J* = 8.3 Hz, Ar), 2.32 (s, 3H, Me), 2.28 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 199.3 (CO), 140.0, 139.6, 139.0 (=CH), 137.2, 131.7, 130.9 (Ar, 2CH), 129.5 (Ar, 2CH), 129.0 (Ar, 4CH), 127.8 (Ar, CH), 27.9 (Me), 21.3 (Me); IR ($CHCl_3$): ν = 2900, 1653 (CO), 1434, 815 cm^{-1}; HRMS (ES): calcd for $C_{17}H_{16}O$ $[M]^+$: 236.1201; found: 236.1199.

α,β-Unsaturated Ketone 44k. 161 mg (0.72 mmol) of α-allenol **43k**, and after chromatography of the residue using hexanes/ethyl acetate (30:1) as eluent gave compound **44k** (80 mg, 50%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.66 (s, 1H, =CH), 7.42 (m, 3H, Ar), 7.18 (m, 5H, Ar), 7.05 (d, 2H, *J* = 7.7 Hz, Ar), 2.33 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 199.3 (CO), 140.9, 138.8 (=CH), 136.9, 134.6, 130.8 (Ar, 2CH), 129.5 (Ar, 2CH), 129.2 (Ar, CH), 129.0 (Ar, 2CH), 128.2 (Ar, 2CH), 127.9 (Ar, CH), 27.9 (Me); IR ($CHCl_3$): ν = 2915, 1660 (CO), 1426, 1024 cm^{-1}; HRMS (ES): calcd for $C_{16}H_{14}O$ $[M]^+$: 222.1045; found: 222.1041.

α,β-Unsaturated Ketone 50a. From 140 mg (0.50 mmol) of α-allenol **49a**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **50a** (79 mg, 57%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.43 (m, 5H), 7.16 (m, 1H), 6.72 (d, 1H, *J* = 7.7 Hz), 6.68 (m, 2H), 3.17 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 204.4, 167.1, 151.8, 145.0, 133.4, 130.5, 130.2, 129.7 (2C), 128.7, 128.3 (2C), 123.6, 122.4, 121.1, 108.7, 29.5, 26.4; IR ($CHCl_3$): ν = 2932, 1705 (CO), 1610 (CO), 1482, 754, 696 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{15}NO_2$ $[M]^+$: 277.1103; found: 277.1093.

α,β-Unsaturated Ketone 50b. From 60 mg (0.23 mmol) of α-allenol **49b**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **50b** (38 mg, 62%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.44 (m, 5H), 7.10 (m, 1H), 6.75 (d, 1H, *J* = 7.7 Hz), 6.66 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.7, 150.4, 147.9, 141.7, 132.9, 131.1, 130.2, 129.9, 129.4 (2C), 127.8 (2C), 123.7, 122.0, 121.5, 109.9, 29.0; IR ($CHCl_3$): ν = 2936, 1706 (CO), 1606 (CO), 1482, 755, 695 cm^{-1}; HRMS (ES): calcd for $C_{17}H_{13}NO_2$ $[M]^+$: 263.0946; found: 263.0956.

α,β-Unsaturated Ketone 50c. From 125 mg (0.38 mmol) of allenol **49c**, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave compound **50c** (63 mg, 49%) as a colorless oil; Colorless oil; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ =

7.50 (m, 4H, Ar), 7.20 (m, 2H, Ar), 6.73 (d, 1H, *J* = 8.3 Hz, Ar), 6.70 (d, 1H, *J* = 2.1 Hz, Ar), 3.24 (s, 3H, NMe), 2.48 (s, 3H, COMe); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 203.4 (CO), 166.4 (CO), 153.0, 143.0, 132.4, 130.3 (Ar, CH), 129.7 (Ar, CH), 129.5 (Ar, 2CH), 128.3 (Ar, CH), 127.7 (Ar, 2CH), 127.4, 123.3 (Ar, CH), 123.0, 122.0, 109.1 (Ar, CH), 28.9 (Me), 26.1 (NMe); IR ($CHCl_3$): ν = 2924, 1707 (CO), 1608 (CO), 1485, 755, 698 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{14}ClNO_2$ [*M*]$^+$: 311.0713; found: 311.0724.

Preparation of α,β-unsaturated ketones 50d and 51d. From 111 mg (0.45 mmol) of α-allenol **49d**, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent, 32 mg (35%) of the less polar compound **50d** and 11 mg (12%) of the more polar compound **51d** were obtained.

α,β-Unsaturated Ketone 50d. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.26 (dd, 1H, *J* = 8.3, 1.9 Hz, Ar), 7.14 (d, 1H, *J* = 2.0 Hz, Ar), 6.74 (d, 1H, *J* = 8.3 Hz, Ar), 3.23 (s, 3H, NMe), 2.62 (s, 3H, Me), 2.50 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 205.2 (CO), 167.3 (CO), 151.6, 141.1, 129.2 (Ar, CH), 127.6, 122.6 (Ar, CH), 121.5, 120.8, 108.9 (Ar, CH), 28.4 (NMe), 25.9 (Me), 15.7 (Me); IR ($CHCl_3$): ν = 2925, 1715 (CO), 1604 (CO), 1475, 756 cm^{-1}; HRMS (ES): calcd for $C_{13}H_{12}ClNO_2$ [*M*]$^+$: 249.0557; found: 249.0567.

α,β-Unsaturated Ketone 51d. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.50 (d, 1H, *J* = 2.0 Hz, Ar), 7.30 (dd, 1H, *J* = 8.3, 1.9 Hz, Ar), 6.77 (d, 1H, *J* = 8.3 Hz, Ar), 3.20 (s, 3H, NMe), 2.49 (s, 3H, Me), 2.36 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 206.3 (CO), 170.3 (CO), 165.9, 142.7, 129.1 (Ar, CH), 127.6, 123.9 (Ar, CH), 123.0, 109.1 (Ar, CH), 28.6 (NMe), 25.9 (Me), 17.4 (Me); IR ($CHCl_3$): ν = 2920, 1706 (CO), 1600 (CO), 1461, 736 cm^{-1}; HRMS (ES): calcd for $C_{13}H_{12}ClNO_2$ [*M*]$^+$: 249.0557; found: 249.0564.

α,β-Unsaturated Ketone 53a. From 94 mg (0.26 mmol) of α-allenol **52a**, and after chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent gave compound **53a** (18 mg, 20%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.30 (s, 1H, NH), 8.12 (m, 2H, Ar), 7.97 (s, 1H, Ar), 7.72 (m, 3H, Ar), 7.49 (m, 3H, Ar + =CH), 7.35 (m, 2H, Ar), 2.36 (s, 3H, COMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 172.8 (CO), 171.3, 129.5 (=CH), 129.1, 128.9 (Ar, 2CH), 128.7 (Ar, CH), 128.1 (Ar, CH), 127.4 (2C), 127.3 (Ar, CH), 125.1 (Ar, CH), 123.2 (Ar, CH), 118.4 (Ar, CH), 115.2 (Ar, CH), 110.7 (Ar, CH), 28.0 (Me); IR ($CHCl_3$): ν = 3370 (NH), 3057, 1734 (CO) 1457, 1152, 754 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{15}NO$ [*M*]$^+$: 261.1154; found: 261.1166.

α,β-Unsaturated Ketone 53b. From 82 mg (0.27 mmol) of α-allenol **52b**, and after chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent gave compound **53b** (19 mg, 26%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.64 (s, 1H, NH), 7.91 (s, 1H, =CH), 7.82 (d, 1H, *J* = 7.1 Hz, Ar), 7.59 (d, 1H, *J* = 2.8 Hz, Ar), 7.46 (d, 1H, *J* = 7.1 Hz, Ar), 7.29 (m, 2H, Ar), 2.55 (s, 3H, COMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 172.6 (CO), 135.4, 132.8, 131.1 (Ar, CH), 129.4, 126.1 (Ar, CH), 124.5, 123.3 (Ar, CH), 120.9 (Ar, CH), 118.5 (Ar, CH), 111.4 (Ar, CH), 25.5 (Me), 19.6 (Me); IR ($CHCl_3$): ν = 3314 (NH), 1708 (CO) 1460, 1245, 748 cm^{-1}; HRMS (ES): calcd for $C_{13}H_{13}NO$ [*M*]$^+$: 199.0997; found: 199.1005.

Typical Procedure for the Iron-Catalyzed Rearrangement Reaction of α-Allenols 43 and 54–56. To a solution of the appropriate allenol **43** or **54–56** (1.0 mmol) in dichloromethane (10 mL), $FeCl_3 \cdot 6H_2O$ (0.10 mmol or 0.20 mmol) was added. The reaction mixture was stirred at reflux temperature until the starting material disappeared as indicated by TLC. After filtration through a pad of Celite, the mixture was concentrated under vacuum, and purified by flash column chromatography eluting with ethyl

acetate/hexanes mixtures. Spectroscopic and analytical data for pure forms of compounds **44**, **48**, and **57–61** follow.

Preparation of α,β-unsaturated ketone 44d and chlorodiene 48d. From 238 mg (0.73 mmol) of allenol **43d**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent, 114 mg (46%) of the less polar compound **48d** and 52 mg (22%) of the more polar compound **44d** were obtained.

Chlorodiene 48d. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.48 (dd, 2H, *J* = 7.0, 1.5 Hz, Ar), 7.36 (td, 2H, *J* = 7.6, 1.6 Hz, Ar), 7.28 (t, 1H, *J* = 7.0 Hz, Ar), 7.15 (m, 3H, Ar), 7.02 (td, 1H, *J* = 7.8, 1.6 Hz, Ar), 6.88 (td, 1H, *J* = 7.6, 1.0 Hz, Ar), 6.81 (dd, 1H, *J* = 8.0, 1.2 Hz, Ar), 6.67 (dd, 1H, *J* = 8.2, 1.0 Hz, Ar), 6.34 (s, 1H, =CH), 5.08 (d, 1H, *J* = 1.1 Hz, =C*H*H), 4.91 (d, 1H, *J* = 1.1 Hz, =CH*H*), 1.92 (d, 3H, *J* = 1.4 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 154.9, 153.8, 139.8, 137.8, 136.2, 133.2, 131.2 (Ar, CH), 130.3 (Ar, CH), 129.7, 129.3 (Ar, 2CH), 128.6 (Ar, CH), 128.3 (Ar, CH), 128.1 (Ar, 2CH), 127.2 (Ar, CH), 124.7 (Ar, CH), 123.7 (Ar, CH), 122.7 (Ar, CH), 119.3 (Ar, CH), 117.7 (=CH), 115.3 (=CH_2), 23.3 (Me); IR ($CHCl_3$): ν = 3060, 1477, 1430, 1228, 744, 694 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{19}ClO$ [*M*]$^+$: 346.1124; found: 346.1138.

Preparation of α,β-unsaturated ketone 44e and chlorodiene 48e. From 340 mg (1.75 mmol) of allenol **43e**, and after chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent, 112 mg (30%) of the less polar compound **48e** and 65 mg (19%) of the more polar compound **44e** were obtained.

Chlorodiene 48e. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.22 (d, 2H, *J* = 8.6 Hz), 7.17 (d, 2H, *J* = 8.8 Hz), 6.21 (d, 1H, *J* = 1.2 Hz), 5.21 (d, 1H, *J* = 1.3 Hz), 5.05 (d, 1H, *J* = 1.3 Hz), 1.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 139.6, 136.3, 135.0, 132.8, 130.0 (2C), 128.3 (2C), 128.1, 115.5, 23.7; IR ($CHCl_3$): ν = 3060, 1478, 745, 692 cm^{-1}; HRMS (ES): calcd for $C_{11}H_{10}Cl_2$ [*M*]$^+$: 212.0160; found: 212.0143.

Preparation of α,β-unsaturated ketone 57a and chlorodiene 58a. From 101 mg (0.33 mmol) of allenol **54a**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent, 10 mg (9%) of the less polar compound **58a** and 8 mg (8%) of the more polar compound **57a** were obtained.

α,β-Unsaturated Ketone 57a. Colorless oil; $[\alpha]_D$ = +32.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.27 (t, 2H, *J* = 7.3 Hz, Ar), 7.00 (t, 1H, *J* = 7.4 Hz, Ar), 6.92 (d, 2H, *J* = 7.9 Hz, Ar), 6.55 (dd, 1H, *J* = 9.4, 1.3 Hz, =CH), 5.45 (d, 1H, *J* = 4.4 Hz, H3), 4.79 (dd, 1H, *J* = 9.4, 4.4 Hz, H4), 3.23 (dd, 1H, *J* = 14.0, 7.7 Hz, NCH*H*), 2.88 (dd, 1H, *J* = 14.0, 6.7 Hz, NC*H*H), 2.23 (s, 3H, COMe), 1.86 (m, 1H, CH isobut), 1.85 (d, 3H, *J* = 1.3 Hz, Me), 0.98 (d, 3H, *J* = 7.4 Hz, Me), 0.95 (d, 3H, *J* = 6.8 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 198.5 (CO), 165.4 (CO), 156.5, 142.8, 134.6 (=CH), 130.7 (Ar, 2CH), 122.5 (Ar, CH) 115.2 (Ar, 2CH), 81.1 (CH, H3), 56.8 (CH, H4), 48.7 (NCH_2), 26.5 (CH isobut), 24.6 (Me), 19.3 (Me), 19.3 (Me); IR ($CHCl_3$): ν = 1757 (CO), 1673 (CO), 1232, 754 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{23}NO_3$ [*M*]$^+$: : 301.1678; found: 301.1682.

Chlorodiene 58a. Colorless oil; $[\alpha]_D$ = +7.8 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.28 (t, 2H, *J* = 7.3 Hz, Ar), 7.01 (t, 1H, *J* = 7.3 Hz, Ar), 6.98 (dd, 2H, *J* = 8.8, 1.1 Hz, Ar), 5.47 (dd, 1H, *J* = 9.8, 1.5 Hz, =CH), 5.45 (d, 1H, *J* = 1.3 Hz, =C*H*H), 5.29 (d, 1H, *J* = 4.4 Hz, H3), 5.14 (d, 1H, *J* = 1.2 Hz, =CH*H*), 4.76 (dd, 1H, *J* = 9.9, 4.5 Hz, H4), 3.16 (dd, 1H, *J* = 14.0, 7.9 Hz, NCH*H*), 2.88 (dd, 1H, *J* = 14.0, 6.7 Hz, NC*H*H), 1.92 (d, 3H, *J* = 1.5 Hz, Me), .1.88 (m, 1H, CH isobut), 0.95 (d, 3H, *J* = 6.9 Hz, Me), 0.92 (d, 3H, *J* = 6.7

Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 165.8 (CO), 157.3, 142.5, 138.1, 129.5 (Ar, 2CH), 123.8 (Ar, CH), 122.2 (=CH), 115.7 (Ar, 2CH), 115.3 (=CH_2), 81.7 (CH, H3), 57.3 (CH, H4), 48.2 (NCH_2), 27.5 (CH isobut), 22. 6 (Me), 20.3 (Me), 20.3 (Me); IR ($CHCl_3$): ν = 3342 (OH), 1758 (CO), 1236, 756 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{22}ClNO_2$ [*M*]$^+$: 319.1339; found: 319.1324.

Preparation of chlorodiene (*E*)-58b and chlorodiene (*Z*)-58b. From 140 mg (0.38 mmol) of allenol **54b**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent, 41 mg (27%) of the less polar compound **(*E*)-58b** and 15 mg (10%) of the more polar compound **(*Z*)-58b** were obtained.

Enol (*E*)-58b. Colorless oil; $[\alpha]_D$ = +23.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.22 (m, 4H, Ar), 7.18 (m, 3H, Ar), 6.91 (d, 2H, *J* = 7.7 Hz, Ar), 6.90 (m, 1H, Ar), 5.96 (d, 1H, *J* = 10.1 Hz, =CH), 5.69 (d, 1H, *J* = 1.0 Hz, =C*H*H), 5.33 (d, 1H, *J* = 4.4 Hz, H3), 5.29 (d, 1H, *J* = 1.2 Hz, =CH*H*), 4.85 (dd, 1H, *J* = 9.9, 4.4 Hz, H4), 3.12 (dd, 1H, *J* = 13.9, 7.6 Hz, NCH*H*), 2.89 (dd, 1H, *J* = 13.9, 6.9 Hz, NC*H*H), 1.86 (sept, 1H, *J* = 6.7 Hz, CH isobut), 0.89 (d, 3H, *J* = 6.7 Hz, Me), 0.86 (d, 3H, *J* = 6.6 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 165.6 (CO), 157.1, 145.9, 136.6, 135.9, 129.5 (Ar, 2CH), 128.8 (Ar, CH), 128.6 (Ar, 2CH), 126.7 (Ar, 2CH), 124.5 (=CH), 122.3 (Ar, CH), 118.6 (=CH_2), 115.5 (Ar, 2CH), 81.8 (CH, H3), 58.0 (CH, H4), 48.6 (NCH_2), 27.6 (CH isobut), 20.3 (Me), 20.3 (Me); IR ($CHCl_3$): ν = 3405 (OH), 3061, 1761 (CO), 1235, 757, 694 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{24}ClNO_2$ [*M*]$^+$: 381.1496; found: 381.1508.

Enol (*Z*)-58b. Colorless oil; $[\alpha]_D$ = +15.4 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.42 (m, 4H, Ar), 7.26 (m, 3H, Ar), 7.14 (d, 2H, *J* = 7.4 Hz, Ar), 7.00 (m, 1H, Ar), 6.30 (d, 1H, *J* = 2.8 Hz, =CH), 5.69 (d, 1H, *J* = 1.6 Hz, =C*H*H), 5.26 (d, 1H, *J* = 1.6 Hz, =CH*H*), 5.08 (d, 1H, *J* = 4.2 Hz, H3), 4.78 (dd, 1H, *J* = 4.1, 2.8 Hz, H4), 3.33 (dd, 1H, *J* = 13.9, 8.0 Hz, NCH*H*), 3.12 (dd, 1H, *J* = 14.0, 6.6 Hz, NC*H*H), 2.00 (m, 1H, CH isobut), 1.04 (d, 3H, *J* = 6.7 Hz, Me), 0.99 (d, 3H, *J* = 6.7 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 165.1 (CO), 156.2, 145.3, 137.1, 132.2, 130.7 (Ar, CH), 129.5 (Ar, CH), 128.8 (Ar, CH), 128.5 (Ar, 2CH), 128.0 (Ar, CH), 127.4 (Ar, CH), 125.6 (Ar, 2CH), 124.9 (=CH), 121.7 (Ar, CH), 120.4 (=CH_2), 88.1 (CH, H3), 60.7 (CH, H4), 48.6 (NCH_2), 27.4 (CH isobut), 20.5 (Me), 20.5 (Me); IR ($CHCl_3$): ν = 3396 (OH), 3062, 1758 (CO), 1231, 760, 699 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{24}ClNO_2$ [*M*]$^+$: 381.1496; found: 381.1481.

α,β-Unsaturated Ketone 57c. From 28 mg (0.08 mmol) of α-allenol **54c**, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave compound **57c** (5 mg, 20%) as a colorless oil; $[\alpha]_D$ = +25.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.30 (m, 6H, Ar), 7.03 (m, 2H, Ar), 6.90 (d, 2H, *J* = 7.9 Hz, Ar), 6.34 (dd, 1H, *J* = 9.5, 1.3 Hz, =CH), 5.41 (d, 1H, *J* = 4.5 Hz, H3), 4.65 (dd, 1H, *J* = 9.5, 4.5 Hz, H4), 4.57 (d, 1H, *J* = 14.8 Hz, NC*H*H), 4.29 (d, 1H, *J* = 14.9 Hz, NCH*H*), 2.06 (s, 3H, COMe), 1.64 (d, 3H, *J* = 1.3 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 198.9 (CO), 164.7 (CO), 156.9, 142.4, 134.8, 134.5 (=CH), 129.6 (Ar, 2CH), 129.0 (Ar, 2CH), 128.7 (Ar, 2CH), 128.3 (Ar, CH), 122.5 (Ar, CH), 115.2 (Ar, 2CH), 81.8 (CH, H3), 55.9 (CH, H4), 45.2 (NCH_2), 25.5 (Me), 11.4 (Me); IR ($CHCl_3$): ν = 3063, 1760 (CO), 1682 (CO), 1234, 754, 699 cm^{-1}; HRMS (ES): calcd for $C_{21}H_{21}NO_3$ [*M*]$^+$: 335.1521; found: 335.1526.

α,β-Unsaturated Ketone 57d. From 12 mg (0.03 mmol) of α-allenol **54d**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **57d** (4 mg, 31%) as a colorless oil; $[\alpha]_D$ = +18.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.31 (d, 2H, *J* = 9.1 Hz, Ar), 6.92 (d, 2H, *J* = 9.2 Hz, Ar), 6.89 (d, 2H, *J* = 9.1 Hz, Ar), 6.82 (d, 2H, *J* = 9.1 Hz, Ar), 6.65 (dd, 1H, *J* = 9.2, 1,3 Hz, =CH), 5.47 (d, 1H, *J* = 4.8 Hz,

H3), 5.17 (dd, 1H, *J* = 9.2, 4.8 Hz, H4), 3.81 (s, 3H, OMe), 3.77 (s, 3H, OMe), 2.26 (s, 3H, Me), 1.97 (d, 3H, *J* = 1.5 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 197.2 (CO), 161.9 (CO), 156.8, 155.1, 151.1, 142.7, 135.3 (=CH), 130.4, 118.3 (Ar, 2CH), 116.5 (Ar, 2CH), 114.7 (Ar, 2CH), 114.6 (Ar, 2CH), 82.0 (CH, H3), 56.4 (CH, H4), 55.6 (OMe), 55. 5. (OMe), 25.7 (Me), 11.9 (Me); IR ($CHCl_3$): ν = 2924, 1755 (CO), 1675 (CO), 1508, 1247, 628 cm^{-1}; HRMS (ES): calcd for $C_{22}H_{23}NO_5$ [*M*]$^+$: 381.1576; found: 381.1578.

α,β-Unsaturated Ketone 59. From 158 mg (0.86 mmol) of α-allenol **55**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **59** (38 mg, 24%) as a colorless oil; $[\alpha]_D$ = +13.0 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 6.56 (dd, 1H, *J* = 7.4, 1,3 Hz, =CH), 4.94 (q, 1H, *J* = 7.5 Hz, OCH), 4.21 (dd, 1H, *J* = 8.2, 6.3 Hz, C*H*H), 3.64 (dd, 1H, *J* = 8.0, 7.6 Hz, CH*H*), 2.35 (s, 3H, COMe), 1.82 (d, 3H, *J* = 1.3 Hz, Me), 1.49 (s, 3H, Me), 1.43 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 199.4 (CO), 139.4 (=CH), 109.9 (2C), 73.1 (O*C*H$_2$), 68.7 (OCH), 26.6 (Me), 25.7 (Me), 25.5 (Me), 11.8 (Me); IR ($CHCl_3$): ν = 2927, 1720 (CO), 1257, 1098 cm^{-1}; HRMS (ES): calcd for $C_{10}H_{16}O_3$ [*M*]$^+$: 184.1099; found: 184.1104.

Preparation of chlorodiene 60 and tricycle 61. From 133 mg (0.42 mmol) of allenol **14**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent, 20 mg (15%) of the less polar compound **61** and 11 mg (7%) of the more polar compound **60** were obtained.

Chlorodiene 60. Colorless oil; $[\alpha]_D$ = –17.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.31 (t, 2H, *J* = 7.5 Hz, Ar), 7.00 (t, 1H, *J* = 7.5 Hz, Ar), 6.96 (d, 2H, *J* = 7.7 Hz, Ar), 6.41 (d, 1H, *J* = 7.3 Hz, =CH), 6.03 (d, 1H, *J* = 3.8 Hz, H1), 5.46 (d, 1H, *J* = 1.5 Hz, =C*H*H), 5.41 (d, 1H, *J* = 1.5 Hz, =CH*H*), 5.14 (dd, 1H, *J* = 8.0, 3.1 Hz, H4), 4.71 (d, 1H, *J* = 4.0 Hz, H2), 4.64 (d, 1H, *J* = 3.2 Hz, H3), 1.98 (d, 3H, *J* = 1.0 Hz, Me), 1.60 (s, 3H, Me), 1.35 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 157.1, 141.4, 135.8, 129.7 (Ar, 2CH), 124.8 (=CH), 121.7 (Ar, CH), 115.3 (Ar, 2CH), 113.6 (=CH$_2$), 111.8, 104.8 (CH, H1), 82.7 (CH, H2), 81.5 (CH, H3), 75.9 (CH, H4), 26.8 (Me), 26.2 (Me), 15.0 (Me); IR ($CHCl_3$): ν = 3475 (OH), 1726, 1492, 1231, 1076, 1020, 756 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{21}ClO_4$ [*M*]$^+$: 336.1128; found: 336.1141.

Tricycle 61. Colorless oil; $[\alpha]_D$ = +38.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.22 (dt, 1H, *J* = 7.6, 1.5 Hz, Ar), 7.14 (t, 1H, *J* = 8.0 Hz, Ar), 6.93 (td, 1H, *J* = 7.5, 1.1 Hz, Ar), 6.80 (dd, 1H, *J* = 8.2, 1.2 Hz, Ar), 5.93 (d, 1H, *J* = 3.6 Hz, H1), 4.72 (m, 1H, H2), 4.71 (m, 2H, =CH$_2$), 4.65 (dd, 1H, *J* = 3.9, 2.0 Hz, H4), 4.51 (d, 1H, *J* = 1.6 Hz, H3), 3.85 (d, 1H, *J* = 3.8 Hz, CH), 1.79 (t, 3H, *J* = 3.1 Hz, Me), 1.57 (s, 3H, Me), 1.36 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 209.0 (CO), 152.9, 128.9 (Ar, CH), 127.9 (Ar, CH), 121.1 (Ar, CH), 119.8, 116.3 (Ar, CH), 111.9, 105.2 (CH, H1), 97.0, 83.3 (CH, H2), 78.8 (CH, H3), 75.7 (CH, H4), 74.1 (=CH$_2$), 40.3 (CH), 26.6 (Me), 26.2 (Me), 16.5 (Me); IR ($CHCl_3$): ν = 2927, 1738 (CO), 1216, 1078, 1015, 757 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{20}O_5$ [*M*]$^+$: 316.1311; found: 316.1298.

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IX. CAPÍTULO 6

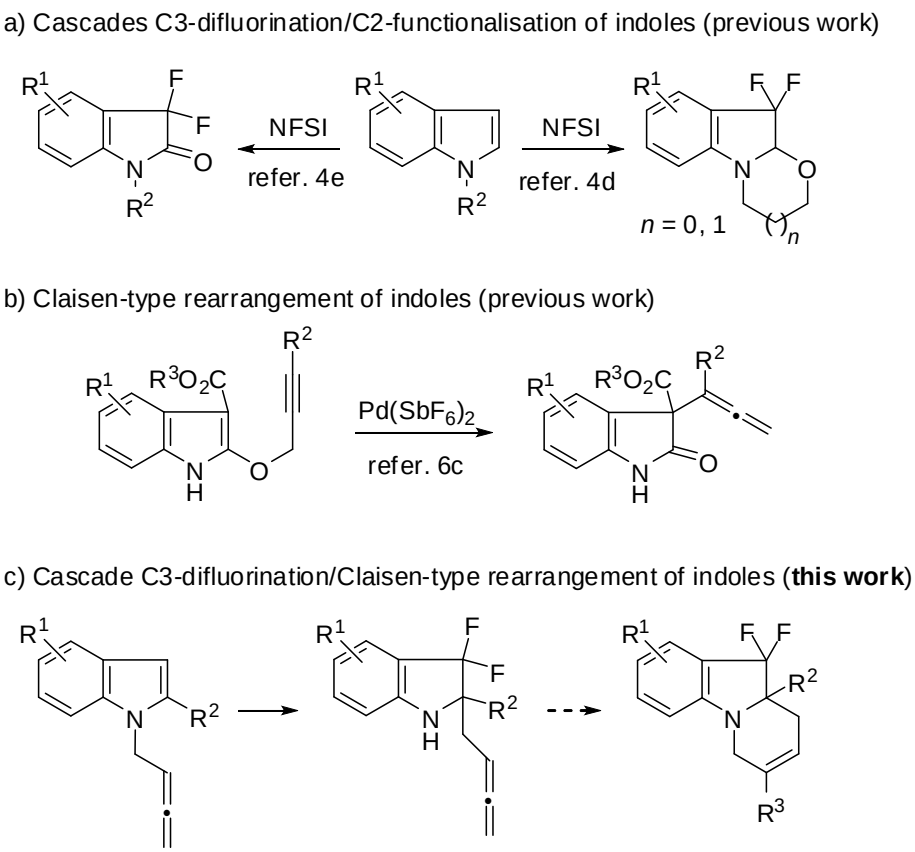
IX.1. Iron-catalyzed domino indole fluorination/allenic aza–Claisen rearrangement

The synthesis of 2-allenyl-2-substituted-3,3-difluoroindolines has been accomplished taking advantage of the reaction between N-allenyl-indoles and Selectfluor under iron catalysis.

Chem. Commun. **2016**, *52*, 6813

IX.2. Communication

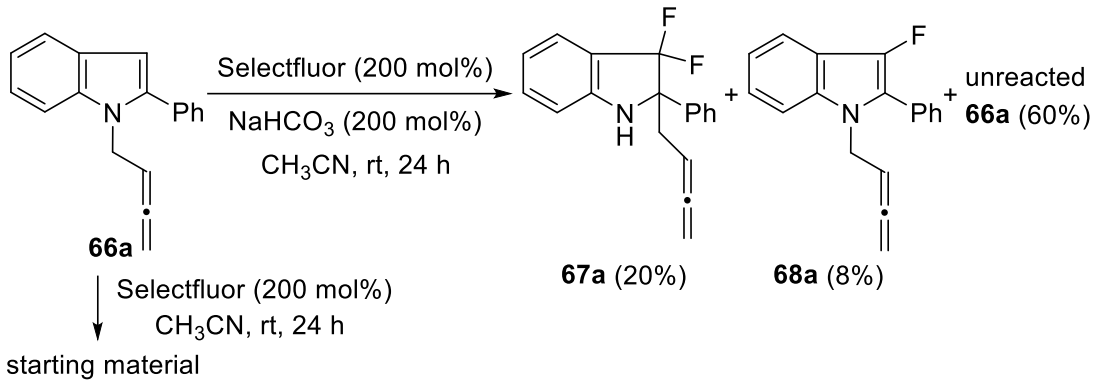
Fluoroorganic molecules feature peculiar biological activities because of their improved lipophilicity and metabolic stability.[1] The difluoromethyl moiety is particularly relevant due to its isopolar and isosteric nature with the $C(CH_3)_2$, C=O or hydroxyl groups.[2] On the other hand, the dearomatization of indoles has received considerable attention in organic synthesis because of the bioactivity of the resulting indolines.[3] Considerable efforts have been devoted to the fluorination of functionalised indoles [Scheme IX.1, Eq. (1a)],[4] because this methodology is a direct entry to diverse fluorinated indoline structures. However, to the best of our knowledge, there is lack of studies of the fluorofunctionalisation of the allenic indole moiety. This is rather surprising taking into account the rich chemistry of the allene moiety.[5]



Scheme IX.1 Indole as platform for difluorination and allenic Claisen-type rearrangement: Previous and current proposals.

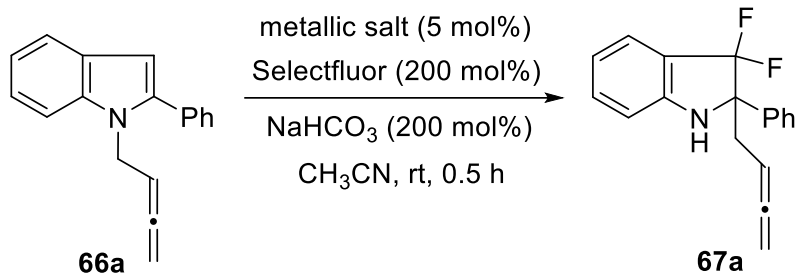
As far as we know, the allene N1–C2 Claisen rearrangement of indoles has not been previously reported, being the C2–C3 Claisen rearrangement of indoles to form allenyl oxindoles the only related precedent [Scheme IX.1, Eq. (1b)].[6] We envisioned that allenic fluorinated indolines could be formed if a rearrangement step is associated to the fluorination sequence. This would be a highly valuable transformation because an additional allene moiety would be installed in the product serving as a platform for further functionalization. Considering the important properties of both polyfluorinated molecules as well as fused indolines, the β-amino 1,2-diene moiety of 2-allenyl-2-substituted-3,3-difluoroindolines may be a useful handle for cyclization reactions, and consequently for the achievement of difluorinated *N*-fused indolines. Herein we report an iron-catalyzed tandem process, namely, fluorination/allenic aza**–**Claisen rearrangement[6] which forms 2-allenyl-2-substituted-3,3-difluoroindolines [Scheme IX.1, Eq. (1c)].

Our initial efforts focused on the application of electrophilic fluorination to the selective construction of difluoroindolines having a quaternary center. Allenic indole **66a** was chosen as a model substrate for the fluorofunctionalisation reaction. Attempts to profitably generate a difluoroindoline structure from **66a** by using Selectfluor without additives failed.[7] A more promising result was encountered through the addition of sodium bicarbonate, although the more of the starting material kept unreacted. Besides, 3,3-difluoroindoline **67a** was isolated along with a minor component, the unstable 3-fluoroindole **68a** (Scheme IX.2).



Scheme IX.2 Reaction of 1-allenyl-2-phenyl-indole **66a** with Selectfluor.

To mitigate the poor reactivity of allenylindole **66a** as well as the formation of intermediate **68a**, we intended the activation of the allene moiety through Lewis acid catalysis (Table IX.1). Initially, in order to get a better result in the formation of product **67a**, we attempted a gold-catalyzed reaction.[8] Fortunately, the addition of [(Ph_3P)$AuNTf_2$] (5 mol%) allow us to efficiently transform in just one hour substrate **66a** into 2-allenyl-2-phenyl-3,3-difluoroindoline **67a** in a totally selective fashion (Table IX.1, entry 1).



Entry	metallic salt	Yield[a]
1	[(Ph_3P)$AuNTf_2$]	83%
2	$PtCl_2$	71%
3	$InCl_3$	63%
4	$HfCl_4$	64%
5	$Fe(OTf)_3$	81%

[a]Yield of pure, isolated product with correct analytical and spectral data.

Table IX.1. Selective fluorination/rearrangement sequence of allenyl indole **66a** under modified metal-catalyzed conditions.

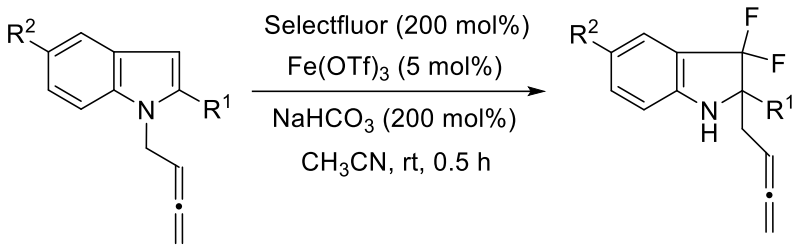
It was interesting at this point to test the catalytic abilities of different metallic salts. The difluorination/rearrangement sequence could also be catalyzed by $PtCl_2$, $InCl_3$, and $HfCl_4$ but with slightly diminished effectiveness. Interestingly, the use of $Fe(OTf)_3$ gave similar results to the Gagosz' catalyst (Table IX.1, entry 5). Taking into account the inexpensiveness and eco-friendliness of iron(III) salts, we decided to develop further the $Fe(OTf)_3$-catalyzed fluoro-rearrangement. When Selectfluor (200 mol%) was used as the fluorination reagent, the spots on the tin-layer chromatographic (TLC) plate of the reaction mixture look very clean. However,

alternative fluorine sources such as *N*-fluorobenzenesulfonimide afforded poorer results. Among all the solvents examined, acetonitrile proved to be the best choice, affording product **67a** in a good 81% yield (Scheme IX.3). The metal-catalysed reaction between indole **66a** and Selectfluor in absence of $NaHCO_3$ did not go to completion, thus highlighting the importance of the base for the success of the difluoroindoline formation.

To explore the effects of various substrates on fluorofunctionalisation reactions, a number of new indole-tethered allenes were synthesized. As shown in Scheme S1 (see Experimental Section), starting materials, allenes **66a–m** were made from the corresponding terminal alkynes **65a–m** by treatment with paraformaldehyde in the presence of diisopropylamine and copper(I) bromide (Crabbé reaction).[9]

With an optimized fluorofunctionalisation system in hand, we investigated the behaviour of 1-(buta-2,3-dienyl)-2-aryl-1*H*-indoles **66b–i**. As shown in Scheme IX.3, all 1-allenyl-2-aryl-substituted substrates exhibited excellent reactivity in the domino indole fluorination/allenic aza–Claisen rearrangement. The steric properties of the substituents in the indole moiety did not affect significantly the reactivity, with *tert*-butylphenyl and naphthalen-2-yl functionalized indoles **66e**,**f** performing well in the difluoroindolines **67e**,**f** formation. Besides, no matter whether electron-withdrawing (such as 4-ClC_6H_4 and 4-FC_6H_4) or electron-donating groups (such as 4-MeC_6H_4) are introduced to the 2-aryl substituent as far as conversions are concerned. The presence of substituents at the benzene fused ring provided the same reactivity pattern independently of the electronic nature, such as in substrates **66g,h**, bearing EDG, or in substrates **66i–k**, bearing EWG. Taking into account all the examples of Scheme IX.3, the reaction proved to be functional group tolerant. Complete conversion was observed by TLC and ^1H NMR analysis of the crude reaction mixtures of indole-tethered allenes **66**, and no side-products were detected. Unfortunately, some decomposition was observed on sensitive fluoroindolines **67** during purification by flash chromatography, which may be responsible for the moderate isolated yields. Nicely, using deactivated silica gel during chromatographic purification resulted in a detectable (5–10%) improvement in the isolated yields of products **67** and **69**. Even more interestingly, nitro- and cyano-derivatives **67j** and **67k** did not require further purification and were obtained in

excellent yields.

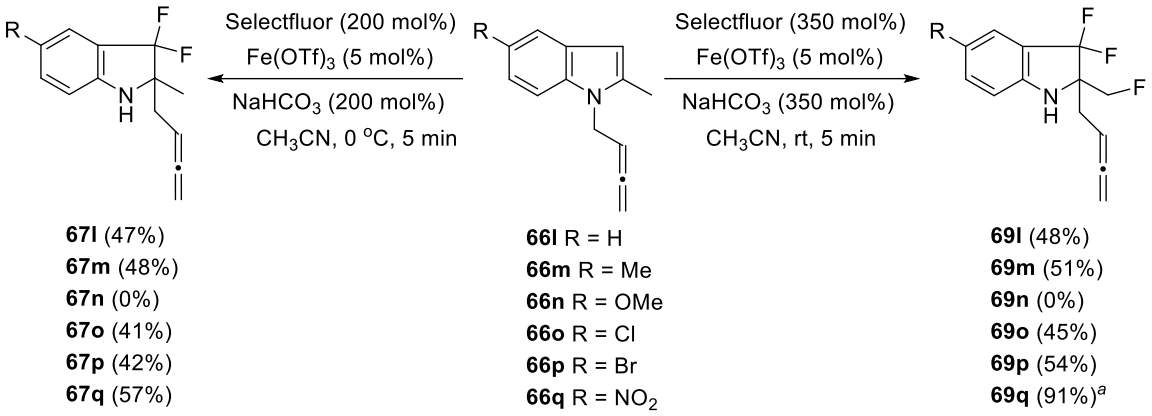


66a R^1 = Ph, R^2 = H	**67a** (83%)
66b R^1 = 4-ClC_6H_4, R^2 = H	**67b** (66%)
66c R^1 = 4-FC_6H_4, R^2 = H	**67c** (40%)
66d R^1 = 4-MeC_6H_4, R^2 = H	**67d** (48%)
66e R^1 = 4-*t*BuC_6H_4, R^2 = H	**67e** (43%)
66f R^1 = naphthalen-2-yl, R^2 = H	**67f** (55%)
66g R^1 = 4-MeC_6H_4, R^2 = Me	**67g** (52%)
66h R^1 = 4-MeC_6H_4, R^2 = OMe	**67h** (42%)
66i R^1 = 4-MeC_6H_4, R^2 = F	**67i** (44%)
66j R^1 = Ph, R^2 = NO_2	**67j** (92%)[a]
66k R^1 = Ph, R^2 = CN	**67k** (97%)[a]

Scheme IX.3 Synthesis of 2-aryl-2-(buta-2,3-dienyl)-3,3-difluoroindolines **67a–i**. [a]Chromatographic purification was not necessary.

Despite its usefulness, the catalytic C–F bond formation at sp^3 carbon centres using electrophilic reagents remains a synthetic challenge, because incorporation of fluorine into sp^3–hybridized carbons is achieved through nucleophilic fluorination reactions.[10] Originally, we were attempting the iron-catalysed difluorofunctionalisation/rearrangement sequence of *N*-allenylindole **66l** under Fe(III) catalysis (5 mol%) in the presence of Selectfluor (200 mol%). The expected product **67l** was the minor component, but, surprisingly, a 20% yield of the trifluoroindoline **69l** was obtained. Consequently, our studies focused on developing a more efficient transformation. The reaction product **69l** could only be obtained in reasonable yield using a higher fluorination reagent loading. Worthy of note, after considerable experimentation we were able to find suitable conditions for the controllable formation of both type of adducts **67** and **69** (Scheme IX.4). 1-Allenyl-2-methyl-indoles **66** on exposure to the system $Fe(OTf)_3$ (5 mol%), $NaHCO_3$ (200 mol%), and Selectfluor (200 mol%) in acetonitrile at 0 °C, exclusively afforded 2-methyl-3,3-difluoroindolines **67** in just 5 minutes. By contrast, the reaction of

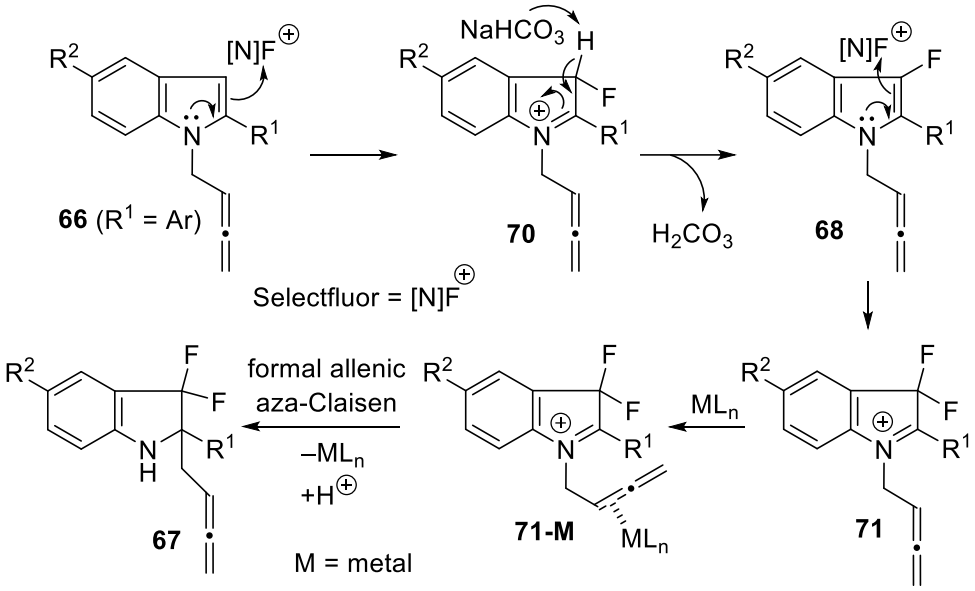
substrates **66** with $Fe(OTf)_3$ (5 mol%), $NaHCO_3$ (350 mol%), and Selectfluor (350 mol%) in acetonitrile at room temperature, did allow the sole formation of 2-fluoromethyl-3,3-difluoroindolines **69**. Unfortunately, compound **66n**, with a methoxy substituent at the C5 indole moiety, only led to several unidentified products upon treatment with Selectfluor. Nitro adduct **69q** did not require further purification and was obtained in nearly quantitative yield.



Scheme IX.4 Synthesis of 2-(buta-2,3-dienyl)-3,3-difluoro-2-methyl indolines **67** and 2-(buta-2,3-dienyl)-2-fluoromethyl-3,3-difluoroindolines **69**. [a]Chromatographic purification was not necessary.

We monitored the reaction of *N*-allenylindole **66b** by both ^{1}H NMR and ^{19}F NMR spectroscopy in order to track the reaction intermediates (Figures IX.S1 and IX.S2, see IX.3. Experimental Section). Because of the paramagnetic character of $Fe(OTf)_3$ we did select $[(Ph_3P)AuNTf_2]$ as catalyst. Unfortunately, results were inconclusive. Although merely speculative at this time, the iron-catalysed generation of 2-(allenyl)-2-aryl-3,3-difluoroindolines **67** should proceed as outlined in Scheme IX.5. Accordingly, we initially propose a Selectfluor-assisted indole monofluorination to form 2-substituted-3-fluoroindoles **68** as represented by intermediate **70**. Taking into account that the reaction does not work without $NaHCO_3$, it may be safe to propose that $NaHCO_3$ should act as a base to facilitate the deprotonation of iminium species **70** to give the aromatic 3-fluoroindoles **68**.[11,12] After delivering the first fluorine atom, again Selectfluor attacks the indole C2–C3 double bond to form difluorospecies **71**. This attack occurs because of the stability of the resulting intermediate iminium cation **71**. Next, the metallic catalyst and **71** forms metal-

coordinate allene **71-M**, further inducing a formal allenic aza–Claisen rearrangement, which liberates 2-substituted-2-(buta-2,3-dienyl)-3,3-difluoroindolines **67** with concomitant regeneration of the catalytic species.

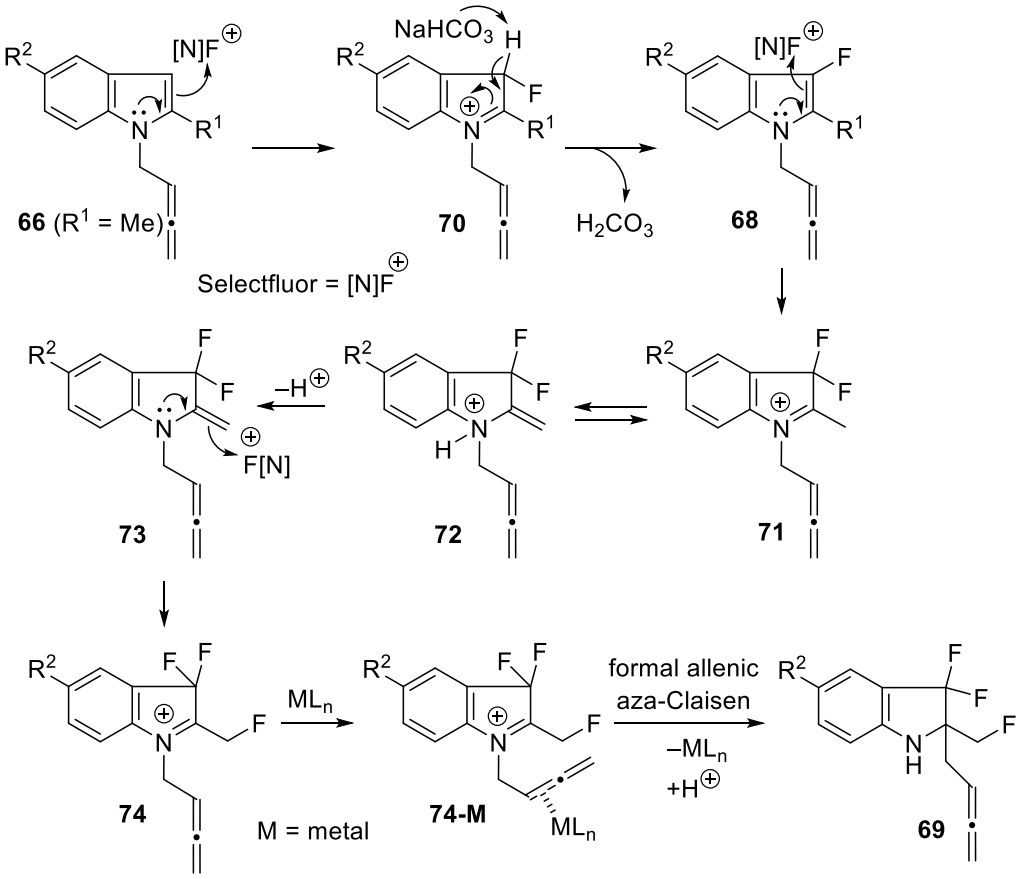


Scheme IX.5 Tentative mechanistic explanation for the Selectfluor-promoted metal-catalyzed synthesis of 2-(allenyl)-2-aryl-3,3-difluoroindolines **67**.

To investigate the reversibility of the fluorination/rearrangement process, 2-(allenyl)-2-phenyl-3,3-difluoroindoline **67a** was treated under metal-catalyzed conditions. Interestingly, it was found that 1-(buta-2,3-dienyl)-3-fluoro-2-phenyl-1*H*-indole **68a** was produced, which may point to a formal retro-allenic aza-Claisen rearrangement process, with the concomitant formation of 3-fluoro-2-phenyl-1*H*-indole, in which a N–C bond cleavage has occurred (Scheme IX.S2, see Experimental Section). This outcome demonstrated that the fluorination/rearrangement sequence had a certain degree of reversibility under the promotion of $[(Ph_3P)AuNTf_2]$ or $Fe(OTf)_3$.

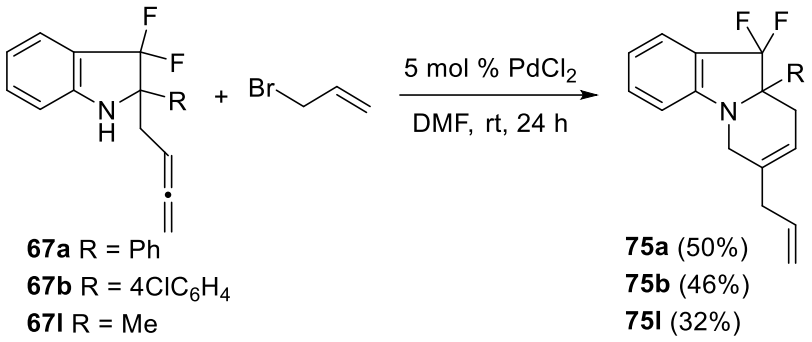
A related pathway for the iron-catalysed generation of 2-(allenyl)-2-fluoromethyl-3,3-difluoroindolines **69** is outlined in Scheme IX.6. A similar scenario to the first and second fluorination can be postulated for the third fluorination, through the attack of Selectfluor to the enamine double bond of **73** to form iminium species **74**. Thus, whereas the 1-(allenyl)-2-aryl-1*H*-indoles exclusively lead to 2-

aryl-3,3-difluoroindoline adducts **67**, the 2-methyl counterparts produce 2-fluoromethyl-3,3-difluoroindoline products **69**.



Scheme IX.6 Tentative mechanistic explanation for the Selectfluor-promoted metal-catalyzed synthesis of 2-(allenyl)-2-fluoromethyl-3,3-difluoroindolines **69**.

N-Fused indolines are widely spread natural products which exhibit relevant biological properties.[13,14] Owing to the efficacy and functional group tolerance of transition metal catalyzed coupling reactions in forming C–heteroatom bonds starting from allenes, we envisioned that our 2-allenyl-3,3-difluoroindolines may be synthetically interesting building blocks for the preparation of *N*-fused indoline derivatives. The carbocyclization–functionalisation of the aminoallene subunit was realized when allyl bromide was added in the palladium-catalyzed transformation of 2-allenyl-1*H*-indoles **67** to generate *N*-fused indolines **75** (Scheme IX.7).



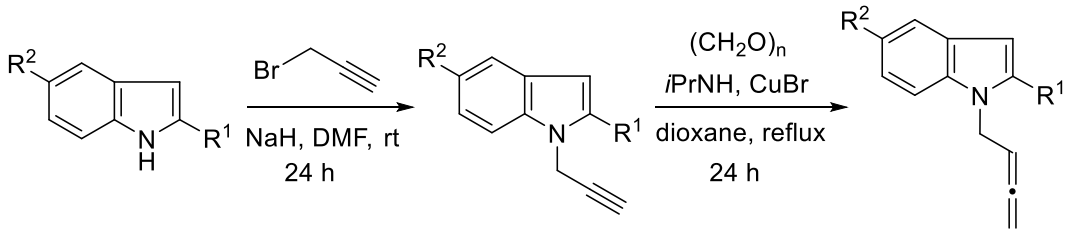
Scheme IX.7 Synthesis of 10,10-difluoro-tetrahydropyrido[1,2-*a*]indoles **75**.

In conclusion, an efficient iron-catalyzed Selectfluor-assisted synthetic route to 2-allenyl-2-substituted-3,3-difluoroindolines from easily accessible *N*-allenyl-indole substrates under mild conditions has been reported. The Fe(III)/Selectfluor system enables the highly selective difluorofunctionalisation/aza–Claisen rearrangement sequence of various 1-allenyl-2-aryl-indoles at ambient temperature. Besides, trifluoroderivatives can be achieved starting from 1-allenyl-2-methyl substrates. Future work could be directed towards the development of an asymmetric version.

IX.3. Experimental Section

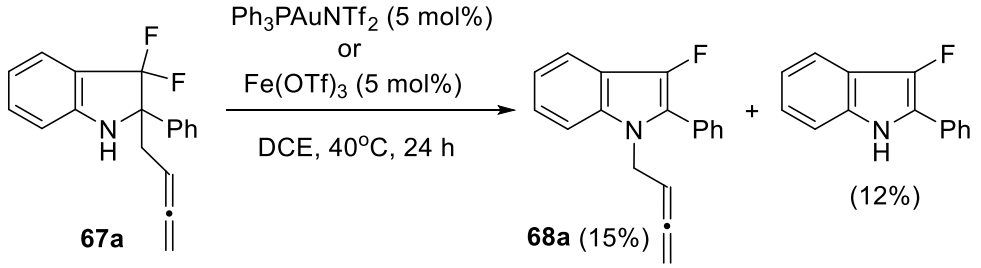
General methods: ^{1}H NMR, ^{19}F NMR, and ^{13}C NMR spectra were recorded on a Bruker Avance-300 or Varian VRX-300S. NMR spectra were recorded in $CDCl_3$ or C_6D_6 solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{1}H, 7.27 ppm; ^{13}C, 76.9 ppm), or C_6D_6 (^{1}H, 7.16 ppm; ^{13}C, 128.0 ppm). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. All commercially available compounds were used without further purification.

2-Substituted indoles were commercially available except 2-(4-tolyl)-1*H*-indole and 2-(4-*tert*-butylphenyl)-1*H*-indole, which were readily obtained as described in the literature: G.-p. Lu, C. Cai, *Synlett* **2012**, *23*, 2992.



R^1 = Ph, R^2 = H	**65a** (82%)	**66a** (84%)
R^1 = 4-ClC_6H_4, R^2 = H	**65b** (73%)	**66b** (73%)
R^1 = 4-FC_6H_4, R^2 = H	**65c** (61%)	**66c** (64%)
R^1 = 4-MeC_6H_4, R^2 = H	**65d** (62%)	**66d** (61%)
R^1 = 4-*t*BuC_6H_4, R^2 = H	**65e** (52%)	**66e** (56%)
R^1 = naphthalen-2-yl, R^2 = H	**65f** (59%)	**66f** (51%)
R^1 = 4-MeC_6H_4, R^2 = Me	**65g** (57%)	**66g** (84%)
R^1 = 4-MeC_6H_4, R^2 = OMe	**65h** (69%)	**66h** (78%)
R^1 = 4-MeC_6H_4, R^2 = F	**65i** (48%)	**66i** (83%)
R^1 = Ph, R^2 = NO_2	**65j** (78%)	**66j** (68%)
R^1 = Ph, R^2 = CN	**65k** (69%)	**66k** (72%)
R^1 = Me, R^2 = H	**65l** (61%)	**66l** (78%)
R^1 = Me, R^2 = Me	**65m** (77%)	**66m** (52%)
R^1 = Me, R^2 = OMe	**65n** (51%)	**66n** (79%)
R^1 = Me, R^2 = Cl	**65o** (71%)	**66o** (86%)
R^1 = Me, R^2 = Br	**65p** (76%)	**66p** (87%)
R^1 = Me, R^2 = NO_2	**65q** (66%)	**66q** (72%)

Scheme IX.S1 Synthesis of 1-(buta-2,3-dienyl)-2-substituted-1*H*-indoles **66a–m**.



Scheme IX.S2 Treatment of 2-(allenyl)-2-phenyl-3,3-difluoroindoline **67a** under metal-catalyzed conditions.

General Procedure for the Preparation of 1-(Prop-2-ynyl)-2-substituted-1*H*-indoles 65. Sodium hydride (1.5 mmol) was added to a solution of the appropriate 2-substituted indole (1.0 mmol) in DMF (15 mL) at 0 °C. After 1 h stirring at rt the solution was cooled at 0 °C and propargyl bromide (1.5 mmol) was added. The reaction was stirred at rt until disappearance of the starting material (TLC). Then water (10 mL) was added, before being being extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/hexanes mixtures gave analytically pure compounds. Spectroscopic and analytical data for some representative pure forms of **65** follow.

1-(Prop-2-ynyl)-2-phenyl-1*H*-indole 65a. From 1.0 g (5.17 mmol) of 2-phenyl-1*H*-indole, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **65a** (1.01 g, 82%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.65 (m, 3H), 7.53 (m, 4H), 7.32 (td, 1H, *J* = 7.0, 1.2 Hz), 7.21 (td, 1H, *J* = 7.8, 1.0 Hz), 6.61 (s, 1H), 4.85 (d, 2H, *J* = 2.5 Hz), 2.39 (t, 1H, *J* = 2.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ: 140.9, 137.6, 132.2, 130.6, 129.3 (2C), 128.7 (2C), 128.2, 122.1, 120.7, 120.5, 110.0, 102.5, 78.9, 72.7, 34.1; IR ($CHCl_3$, cm^{-1}): ν 3291; HRMS (ES): calcd for $C_{17}H_{13}N$ [*M*]$^+$: 231.1042; found: 231.1042.

1-(Prop-2-ynyl)-2-(4-chlorophenyl)-1*H*-indole 65b. From 250 mg (1.10 mmol) of 2-(4-chlorophenyl)-1*H*-indole, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **65b** (213 mg, 73%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.55 (d, 1H, *J* = 7.7 Hz), 7.38 (m, 5H), 7.22 (td, 1H, *J* = 7.1, 1.2 Hz), 7.12 (m, 1H), 6.49 (s, 1H), 4.70 (d, 2H, *J* = 2.5 Hz), 2.29 (t, 1H, *J* = 2.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ: 139.6; 137.6; 13.3; 131.8; 130.6; 130.4; 129.0 (2C); 128.1; 122.4; 120.8; 120.6; 110.0; 102.8; 78.7; 73.0; 34.0; IR ($CHCl_3$, cm^{-1}): ν 3293; HRMS (ES): calcd for $C_{17}H_{12}ClN$ [*M*]$^+$: 265.0652; found: 265.0657.

1-(Prop-2-ynyl)-2-(4-fluorophenyl)-1*H*-indole 65c. From 200 mg (0.9 mmol) of 2-(4-fluorophenyl)-1*H*-indole, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **65c** (136 mg, 61%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.73 (d, 1H, *J* = 7.7 Hz), 7.66 (m, 2H), 7.59 (d, 1H, *J* = 8.2 Hz), 7.38 (dt, 1H, *J* = 7.4, 1.2 Hz), 7.30 (t, 3H, *J* = 7.2 Hz), 6.63 (s, 1H), 4.86 (d, 2H, *J* = 2.5 Hz), 2.45 (t, 1H, *J* = 2.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ: 139.8, 137.5, 131.0, 130.9, 128.3 (2C), 122.3, 120.7, 116.0, 115.9, 115.7, 115.6, 110.0, 109.9, 105.6, 78.8, 33.9; ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –113.5 (s, 1F); IR ($CHCl_3$, cm^{-1}): ν 3292; HRMS (ES): calcd for $C_{17}H_{12}FN$ [*M*]$^+$: 249.0948; found: 249.0943.

1-(Prop-2-ynyl)-2-(4-methylphenyl)-1*H*-indole 65d. From 207 mg (0.99 mmol) of 2-(4-methylphenyl)-1*H*-indole, and after chromatography of the residue using hexanes/ethyl acetate (7:1) as eluent gave compound **65d** (151 mg, 62%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.55 (d, 1H, *J* = 7.9 Hz), 7.38 (m, 3H), 7.16 (m, 4H), 6.47 (d, 1H, *J* = 0.4 Hz), 4.73 (d, 2H, *J* = 2.5 Hz); 2.35 (s, 3H), 2.27 (t, 1H, *J* = 2.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ: 141.1, 138.2, 137.5, 130.5, 129.5 (2C), 129.2 (2C), 128.4, 122.0, 120.6, 120.5, 110.0, 102.2, 79.0, 72.7, 34.1, 21.4; IR ($CHCl_3$, cm^{-1}): ν 3290; HRMS (ES): calcd for $C_{18}H_{15}N$ [*M*]$^+$: 245.1198; found: 245.1201.

1-(Prop-2-ynyl)-2-(4-*tert*-butylphenyl)-1*H*-indole 65e. From 310 mg (1.24 mmol) of 2-(4-*tert*-butylphenyl)-1*H*-indole, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **65e** (184 mg, 52%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.52 (d, 2H, *J* = 8.6 Hz), 7.45 (m, 2H), 7.20 (m, 1H), 7.08 (m, 3H), 6.48 (d, 1H, *J* = 0.7 Hz), 4.75 (d, 2H, *J* = 2.5 Hz), 2.30 (t, 1H, *J* = 2.5 Hz); 1.31 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ: 151.3, 150.1, 141.0, 137.6, 137.1, 129.0,

127.6, 125.7, 122.0, 120.6, 120.5, 110.0, 102.2, 90.7, 79.1, 72.7, 34.8, 34.1, 31.4 (3C); IR ($CHCl_3$, cm^{-1}): ν 3291; HRMS (ES): calcd for $C_{21}H_{21}N$ $[M]^+$: 287.1668; found: 287.1684.

1-(Prop-2-ynyl)-2-(naphthalen-2-yl)-1*H*-indole 65f. From 200 mg (0.82 mmol) of 2-(naphthalen-2-yl)-1*H*-indole, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **65f** (135 mg, 59%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ: 8.00 (s, 1H), 7.69 (m, 2H), 7.64 (m, 3H), 7.43 (d, 1H, *J* = 8.1 Hz), 7.27 (m, 4H), 6.64 (d, 1H, *J* = 0.5 Hz), 4.30 (d, 2H, *J* = 2.5 Hz), 1.83 (t, 1H, *J* = 2.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ: 140.9, 138.4, 133.9, 133.3, 130.3, 130.2, 129.1, 128.7, 128.6, 128.5, 127.2, 126.7, 126.6, 122.6, 121.2, 121.0, 110.5, 103.6, 79.3, 72.8, 33.9; IR ($CHCl_3$, cm^{-1}): ν 3292; HRMS (ES): calcd for $C_{21}H_{15}N$ $[M]^+$: 287.1198; found: 287.1207.

5-Methyl-1-(prop-2-ynyl)-2-(4-methylphenyl)-1*H*-indole 65g. From 247 mg (1.12 mmol) of 5-methyl-2-(4-methylphenyl)-1*H*-indole, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **65g** (166 mg, 57%) as a colorless solid; mp 108–109 °C (*n*-hexane/ethyl acetate); ^{1}H-NMR (300 MHz, acetone-d_6, 25 °C) δ: 7.52 (d, 2H, *J* = 8.2 Hz, Ar), 7.43 (d, 1H, *J* = 8.3 Hz, Ar), 7.36 (m, 1H, Ar), 7.34 (d, 2H, *J* = 8.5 Hz, Ar), 7.06 (dd, 1H, *J* = 8.3, 1.2 Hz, Ar), 6.46 (d, 1H, *J* = 0.7 Hz, Ar), 4.92 (d, 1H, *J* = 2.5 Hz, NCH_2), 2.90 (t, 1H, *J* = 2.5 Hz, ≡CH), 2.41 (s, 3H, Me), 2.40 (s, 3H, Me); ^{13}C-NMR (75 MHz, acetone-d_6, 25 °C) δ: 141.8, 138.8, 137.2, 130.5, 130.3 (Ar, 2CH), 130.0, 129.8, 129.7 (Ar, 2CH), 124.2 (Ar, CH), 121.0 (Ar, CH), 110.9 (Ar, CH), 102.5 (Ar, CH), 80.3, 74.1 (≡CH), 34.5 (NCH_2), 21.6 (Me), 21.3 (Me); IR ($CHCl_3$, cm^{-1}): ν 2919, 1474, 1330, 1163, 823, 789, 643; HRMS (ES): calcd for $C_{19}H_{17}N$ $[M]^+$: 259.1355; found: 259.1354.

5-Methoxy-1-(prop-2-ynyl)-2-(4-methylphenyl)-1*H*-indole 65h. From 159 mg (0.67 mmol) of 5-methoxy-2-(4-methylphenyl)-1*H*-indole, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **65h** (127 mg, 69%) as a colorless solid; mp 115–116 °C (*n*-hexane/ethyl acetate); ^{1}H-NMR (300 MHz, acetone-d_6, 25 °C) δ: 7.51 (d, 2H, *J* = 8.2 Hz, Ar), 7.44 (d, 1H, *J* = 8.8 Hz, Ar), 7.33 (d, 2H, *J* = 7.9 Hz, Ar), 7.10 (d, 1H, *J* = 2.5 Hz, Ar), 6.89 (dd, 1H, *J* = 8.8, 2.5 Hz, Ar), 6.48 (s, 1H, Ar), 4.90 (d, 1H, *J* = 2.5 Hz, NCH_2), 3.81 (s, 3H, OMe), 2.90 (t, 1H, *J* = 2.5 Hz, ≡CH), 2.40 (s, 3H, Me); ^{13}C-NMR (75 MHz, acetone-d_6, 25 °C) δ: 155.8, 142.3, 138.8, 133.9, 130.5, 130.3 (Ar, 2CH), 129.9, 129.8, 129.7 (Ar, 2CH), 112.7 (Ar, CH), 111.8 (Ar, CH), 103.0 (Ar, CH), 102.8 (Ar, CH), 80.3, 74.1 (≡CH), 55.9 (OMe), 34.6 (NCH_2), 21.3 (Me); IR ($CHCl_3$, cm^{-1}): ν 2852, 1619, 1474, 1216, 824, 740, 651; HRMS (ES): calcd for $C_{19}H_{17}NO$ $[M]^+$: 275.1304; found: 275.1319.

5-F*luoro*-1-(prop-2-ynyl)-2-(4-methylphenyl)-1*H*-indole 65i. From 168 mg (0.75 mmol) of 5-fluoro-2-(4-methylphenyl)-1*H*-indole, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **65i** (94 mg, 48%) as a colorless solid; mp 113–114 °C (*n*-hexane/ethyl acetate); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.46 (d, 2H, *J* = 8.2 Hz, Ar), 7.38 (m, 1H, Ar), 7.28 (d, 2H, *J* = 8.0 Hz, Ar), 7.19 (d, 1H, *J* = 2.5 Hz, Ar), 6.98 (m, 1H, Ar), 6.48 (s, 1H, Ar), 4.80 (d, 1H, *J* = 2.6 Hz, NCH_2), 2.41 (s, 3H, Me), 2.38 (t, 1H, *J* = 2.5 Hz, ≡CH); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ: 159.9, 156.8, 142.6, 138.4, 134.0, 130.3, 129.5 (Ar, 2CH), 129.0 (Ar, 2CH), 110.0 (Ar, CH), 109.9 (Ar, CH), 105.7 (Ar, CH), 101.9 (Ar, CH), 78.7, 73.7 (≡CH), 34.1 (NCH_2), 21.3 (Me); IR ($CHCl_3$, cm^{-1}): ν 2921, 1621, 1472, 1197, 824, 783, 645; HRMS (ES): calcd for $C_{18}H_{14}FN$ $[M]^+$: 263.1104; found: 263.1107.

5-Nitro-2-phenyl-1-(prop-2-ynyl)-1*H*-indole 65j. From 200 mg (0.84 mmol) of 5-nitro-2-phenyl-1*H*-indole, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **65j** (181 mg, 78%) as a colorless solid; mp 119–

120 °C (*n*-hexane/ethyl acetate); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 8.60 (d, 1H, *J* = 2.2 Hz, Ar), 8.20 (dd, 1H, *J* = 9.1, 2.3 Hz, Ar), 7.57 (m, 6H, Ar), 6.74 (s, 1H, Ar), 4.87 (d, 2H, *J* = 2.5 Hz, NCH_2), 2.46 (t, 1H, *J* = 2.5 Hz, ≡CH); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 144.1, 142.4, 140.1, 130.9, 129.3 (Ar, 2CH), 129.1 (Ar, CH), 129.0 (Ar, 2CH), 127.5, 117.7 (Ar, CH), 117.6 (Ar, CH), 110.0 (Ar, CH), 104.3 (Ar, CH), 77.7, 73.7 (≡CH), 34.4 (NCH_2); IR ($CHCl_3$, cm^{-1}): ν 2923, 1616, 1468, 1190, 834, 789, 640; HRMS (ES): calcd for $C_{17}H_{12}N_2O_2$ $[M]^+$: 276.0893; found: 276.0888.

2-Phenyl-1-(prop-2-ynyl)-1*H*-indole-5-carbonitrile 65k. From 120 mg (0.54 mmol) of 2-phenyl-1*H*-indole-5-carbonitrile, and after chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent gave compound **65k** (95 mg, 69%) as a pale yellow solid; mp 115–116 °C (*n*-hexane/ethyl acetate); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.88 (t, 1H, *J* = 0.8 Hz, Ar), 7.44 (m, 7H, Ar), 6.54 (s, 1H, Ar), 4.75 (d, 1H, *J* = 2.5 Hz, NCH_2), 2.34 (t, 1H, *J* = 2.5 Hz, ≡CH); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 143.2, 138.9, 131.0, 129.3 (Ar, 2CH), 128.9 (Ar, CH), 128.9 (Ar, 2CH), 128.0, 126.0 (Ar, CH), 125.0 (Ar, CH), 120.6, 110.9 (Ar, CH), 103.6, 102.9 (Ar, CH), 77.8, 73.6 (≡CH), 34.2 (NCH_2); IR ($CHCl_3$, cm^{-1}): ν 2919, 1613, 1467, 1170, 820, 760, 670; HRMS (ES): calcd for $C_{18}H_{12}N_2$ $[M]^+$: 256.0995; found: 256.1007.

1-(Prop-2-ynyl)-2-methyl-1*H*-indole 65l. From 1.0 g (7.63 mmol) of 2-methyl-1*H*-indole, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **65l** (769 mg, 61%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.47 (d, 1H, *J* = 7.7 Hz), 7.28 (d, 1H, *J* = 8.2 Hz), 7.10 (m, 2H), 6.21 (br s, 1H), 4.74 (d, 2H, *J* = 2.5 Hz), 2.42 (s, 3H), 2.19 (t, 1H, *J* = 2.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 136.5, 136.0, 128.3, 120.9, 119.8 (2C), 108.8, 100.9, 78.2, 72.1, 32.3, 12.5; IR ($CHCl_3$, cm^{-1}): ν 3295; HRMS (ES): calcd for $C_{12}H_{11}N$ $[M]^+$: 169.0885; found: 169.0888.

2,5-Dimethyl-1-(prop-2-ynyl)-1*H*-indole 65m. From 500 mg (3.44 mmol) of 2,5-dimethyl-1*H*-indole, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **65m** (485 mg, 77%) as a colorless solid; mp 110–111 °C (*n*-hexane/ethyl acetate); ^{1}H-NMR (300 MHz, acetone-d_6, 25 ^{o}C) δ: 7.30 (d, 1H, *J* = 8.3 Hz, Ar), 7.23 (s, 1H, Ar), 6.93 (d, 1H, *J* = 8.3 Hz, Ar), 6.15 (s, 1H, Ar), 4.94 (d, 1H, *J* = 2.5 Hz, NCH_2), 2.79 (t, 1H, *J* = 2.5 Hz, ≡CH), 2.46 (s, 3H, Me), 2.37 (s, 3H, Me); ^{13}C-NMR (75 MHz, acetone-d_6, 25 ^{o}C) δ: 137.2, 136.2, 129.7, 129.1, 122.9 (Ar, CH), 120.3 (Ar, CH), 109.7 (Ar, CH), 101.1 (Ar, CH), 80.0, 73.4 (≡CH), 32.8 (NCH_2), 21.6 (Me), 12.6 (Me); IR ($CHCl_3$, cm^{-1}): ν 2943, 1632, 1471, 1234, 820, 763, 675; HRMS (ES): calcd for $C_{13}H_{13}N$ $[M]^+$: 183.1078; found: 183.1041.

5-Methoxy-2-methyl-1-(prop-2-ynyl)-1*H*-indole 65n. From 500 mg (3.10 mmol) of 5-methoxy-2-methyl-1*H*-indole, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **65n** (315 mg, 51%) as a colorless solid; mp 119–120 °C (*n*-hexane/ethyl acetate); ^{1}H-NMR (300 MHz, acetone-d_6, 25 ^{o}C) δ: 7.31 (d, 1H, *J* = 8.9 Hz, Ar), 6.97 (d, 1H, *J* = 2.3 Hz, Ar), 6.76 (dd, 1H, *J* = 8.9, 2.5 Hz, Ar), 6.17 (s, 1H, Ar), 4.94 (d, 1H, *J* = 2.5 Hz, NCH_2), 3.77 (s, 3H, OMe), 2.80 (t, 1H, *J* = 2.5 Hz, ≡CH), 2.45 (s, 3H, Me); ^{13}C-NMR (75 MHz, acetone-d_6, 25 ^{o}C) δ: 155.3, 137.7, 132.6, 129.9, 111.1 (Ar, CH), 110.6 (Ar, CH), 102.7 (Ar, CH), 101.3 (Ar, CH), 79.9, 73.4 (≡CH), 55.9 (OMe), 32.9 (NCH_2), 12.6 (Me); IR ($CHCl_3$, cm^{-1}): ν 2958, 1483, 1201, 849, 779; HRMS (ES): calcd for $C_{13}H_{13}NO$ $[M]^+$: 199.0991; found: 199.1004.

5-Chloro-2-methyl-1-(prop-2-ynyl)-1*H*-indole 65o. From 500 mg (3.08 mmol) of 5-chloro-2-methyl-1*H*-indole, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **65o** (444 mg, 71%) as a colorless solid; mp 127–128 °C (*n*-hexane/ethyl acetate); ^{1}H-NMR (300 MHz, acetone-d_6, 25 ^{o}C) δ: 7.47 (s, 1H, Ar),

7.45 (d, 1H, *J* = 8.6 Hz, Ar), 7.10 (dd, 1H, *J* = 8.8, 2.2 Hz, Ar), 6.26 (s, 1H, Ar), 5.00 (d, 1H, *J* = 2.5 Hz, NCH_2), 2.85 (t, 1H, *J* = 2.5 Hz, ≡CH), 2.49 (d, 3H, *J* = 0.9 Hz, Me); ^{13}C-NMR (75 MHz, acetone-d_6, 25 °C) δ: 139.2, 136.1, 130.5, 125.7, 121.4 (Ar, CH), 119.7 (Ar, CH), 111.4 (Ar, CH), 101.2 (Ar, CH), 79.4, 73.9 (≡CH), 33.0 (NCH_2), 12.6 (Me); IR ($CHCl_3$, cm^{-1}): ν 2911, 1621, 1478, 1190, 827, 763, 640; HRMS (ES): calcd for $C_{12}H_{10}NCl$ [*M*]$^+$: 203.0496; found: 203.0502.

5-Bromo-2-methyl-1-(prop-2-ynyl)-1*H*-indole 65p. From 400 mg (1.90 mmol) of 5-bromo-2-methyl-1*H*-indole, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **65p** (359 mg, 76%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.66 (d, 1H, *J* = 1.6 Hz, Ar), 7.26 (m, 2H, Ar), 6.24 (s, 1H, Ar), 4.79 (d, 2H, *J* = 2.5 Hz, NCH_2), 2.49 (s, 3H, Me), 2.30 (t, 1H, *J* = 2.5 Hz, ≡CH); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ: 137.4, 135.1, 130.0, 123.7 (Ar, CH), 122.3 (Ar, CH), 113.1, 110.3 (Ar, CH), 100.5 (Ar, CH), 77.7, 72.5 (≡CH), 32.5 (NCH_2), 12.5 (Me); IR ($CHCl_3$, cm^{-1}): ν 2965, 1497, 1254, 850; HRMS (ES): calcd for $C_{12}H_{10}BrN$ [*M*]$^+$: 246.9991; found: 246.9994.

2-Methyl-5-nitro-1-(prop-2-ynyl)-1*H*-indole 65q. From 500 mg (2.84 mmol) of 2-methyl-5-nitro-1*H*-indole, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound **65q** (404 mg, 66%) as a colorless solid; mp 97–99 °C (*n*-hexane/ethyl acetate); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ: 8.45 (d, 1H, *J* = 2.2 Hz, Ar), 8.08 (dd, 1H, *J* = 9.1, 2.2 Hz, Ar), 7.35 (d, 1H, *J* = 9.1 Hz, Ar), 6.44 (s, 1H, Ar), 4.85 (d, 2H, *J* = 2.5 Hz, NCH_2), 2.52 (s, 3H, Me), 2.35 (t, 1H, *J* = 2.5 Hz, ≡CH); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ: 141.9, 139.6, 139.3, 127.5, 116.8 (Ar, CH), 108.7 (Ar, CH), 103.1 (Ar, CH), 77.4, 73.2 (≡CH), 32.9 (NCH_2), 12.7 (Me); IR ($CHCl_3$, cm^{-1}): ν 2956, 1490, 1234, 832; HRMS (ES): calcd for $C_{12}H_{10}N_2O_2$ [*M*]$^+$: 214.0736; found: 214.0733.

General Procedure for the Cu-Catalyzed Reaction of 1-(Prop-2-ynyl)-2-substituted-1*H*-indoles 65. Preparation of 1-(Buta-2,3-dienyl)-2-substituted-1*H*-indoles 66. A well stirred solution of $(CH_2O)_n$ (0.5 mmol), CuI (0.1 mmol), the appropriate 1-(prop-2-ynyl)-2-substituted-1*H*-indole (0.2 mmol), and *N*,*N*-diisopropylethylamine (Hüning's base) (0.36 mmol) in dioxane (1 mL) was refluxed under argon atmosphere. When the reaction was complete as monitored by TLC, it was cooled to RT. Water (5 mL) was added before being extracted with ethyl acetate (3 x 15 mL). The organic phase was washed with water (2 x 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds **65**. Spectroscopic and analytical data for some representative pure forms of **66** follow.

1-(Buta-2,3-dienyl)-2-phenyl-1*H*-indole 66a. From 266 mg (1.15 mmol) of alkyne **65a**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **66a** (236 mg, 84%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.67 (d, 1H, *J* = 7.7 Hz), 7.57 (t, 1H, *J* = 2.0 Hz), 7.55 (m, 1H), 7.45 (m, 4H), 7.27 (td, 1H, *J* = 7.0, 1.2 Hz), 7.18 (td, 1H, *J* = 7.8, 0.9 Hz), 6.58 (br s, 1H), 5.33 (m, 1H), 4.78 (d, 2H, *J* = 2.8 Hz), 4.77 (s, 2 H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ: 208.5, 141.3, 137.7, 132.8, 129.4 (2C), 128.5 (2C), 128.2, 128.0, 121.7, 120.5, 120.0, 110.3, 102.2, 88.1, 77.3, 42.9; IR ($CHCl_3$, cm^{-1}): ν 1956; HRMS (ES): calcd for $C_{18}H_{15}N$ [*M*]$^+$: 245.1198; found: 245.1199.

1-(Buta-2,3-dienyl)-2-(4-chlorophenyl)-1*H*-indole 66b. From 290 mg (1.10 mmol) of alkyne **65b**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **66b** (224 mg, 73%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.67 (d, 1H, *J* = 7.7 Hz), 7.57 (t, 1H, *J* = 2.0 Hz), 7.55 (m, 1H), 7.45 (m, 4H), 7.27 (td, 1H, *J* = 7.0, 1.2 Hz), 7.18 (td, 1H, *J* = 7.8, 0.9 Hz), 6.58 (br s, 1H), 5.33 (m, 1H), 4.78 (d, 2H, *J* = 2.8 Hz), 4.77 (s, 2 H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ: 208.5, 141.3, 137.7,

132.8, 129.4 (2C), 128.5 (2C), 128.2, 128.0, 121.7, 120.5, 120.0, 110.3, 102.2, 88.1, 77.3, 42.9; IR ($CHCl_3$, cm^{-1}): ν 1954; HRMS (ES): calcd for $C_{18}H_{14}ClN$ $[M]^+$: 279.0809; found: 279,0812.

1-(Buta-2,3-dienyl)-2-(4-fluorophenyl)-1*H*-indole 66c. From 200 mg (0.90 mmol) of alkyne **65c**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **66c** (136 mg, 64%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.70 (d, 1H, *J* = 7.0 Hz), 7.27 (m, 3H), 7.21 (m, 2H), 6.82 (t, 2H, *J* = 8.6Hz), 6.50 (s, 1H), 4.89 (q, 1H, *J* = 5.9 Hz), 4.39 (m, 2H), 4.21(m, 2H); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 208.4, 140.0, 138.3, 131.4, 131.2, 129.4, 128.9, 127.8, 122.3, 121.1, 120.6, 115.8, 115.5, 110.6, 102.9, 88.4, 77.7, 42.5; ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –113.5 (s, 1F); IR ($CHCl_3$, cm^{-1}): ν 1955; HRMS (ES): calcd for $C_{18}H_{14}FN$ $[M]^+$: 263.1104; found: 263.1108.

1-(Buta-2,3-dienyl)-2-(4-methylphenyl)-1*H*-indole 66d. From 150 mg (0.61 mmol) of alkyne **65d**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound **66d** (96 mg, 61%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.54 (m, 1H), 7.32 (m, 3H), 7.12 (m, 4H, 6.44 (d, 1H, *J* = 0.8 Hz), 5.22 (m, 1H), 4.65 (m, 4H), 2.34 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 208.6, 141.4, 138.0, 137.7, 129.9, 129.3 (2C), 129.2 (2C), 128.3, 121.6, 120.5, 120.0, 110.3, 101.9, 88.2, 77.4, 42.9, 21.3; IR ($CHCl_3$, cm^{-1}): ν 1955; HRMS (ES): calcd for $C_{19}H_{17}N$ $[M]^+$: 259.1355; found: 259.1365.

1-(Buta-2,3-dienyl)-2-(4-*tert*-butylphenyl)-1*H*-indole 66e. From 149 mg (0.52 mmol) of alkyne **65e**, and after chromatography of the residue using hexanes/ethyl acetate (70:1) as eluent gave compound **66e** (88 mg, 56%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.55 (m, 2H), 7.35 (m, 3H), 7.10 (m, 3H), 6.45 (d, 1H, *J* = 0.7 Hz), 5.21 (m, 1H), 4.66 (m, 4H), 1.30 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 208.6, 151.1, 141.4, 137.7, 130.3, 129.1 (2C), 125.5 (2C), 121.6, 120.5, 119.9, 110.3, 101.9, 91.0, 88.3, 77.3, 43.0, 34.7, 31.4 (3C); IR ($CHCl_3$, cm^{-1}): ν 1954; HRMS (ES): calcd for $C_{22}H_{23}N$ $[M]^+$: 301.1824; found: 301.1822.

1-(Buta-2,3-dienyl)-2-(naphthalen-2-yl)-1*H*-indole 66f. From 133 mg (0.47 mmol) of alkyne **65f**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **66f** (64 mg, 51%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.92 (s, 1H), 7.75 (m, 1H), 7.64 (m, 3H), 7.56 (dd, 1H, *J* = 6.9, 1.5 Hz), 7.31 (m, 5H), 6.70 (s, 1H), 5.00 (q, 1H, *J* = 6.4 Hz), 4.43 (m, 2H), 4.35 (m, 2H); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 208.5, 141.3, 138.6, 133.8, 133.3, 130.8, 129.2, 128.6 (2C), 128.5, 128.4, 127.5, 126.7, 126.5, 122.3, 121.2, 120.6, 110.6, 103.4, 88.6, 77.3, 42.9; IR ($CHCl_3$, cm^{-1}): ν 1958; HRMS (ES): calcd for $C_{22}H_{17}N$ $[M]^+$: 295.1355; found: 295.1358.

1-(Buta-2,3-dienyl)-5-methyl-2-(4-methylphenyl)-1*H*-indole 66g. From 126 mg (0.49 mmol) of alkyne **65g**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **66g** (112 mg, 84%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.17 (d, 2H, *J* = 8.0 Hz, Ar), 7.04 (m, 4H, Ar), 6.81 (dd, 1H, *J* = 8.5, 1.8 Hz, Ar), 6.20 (d, 1H, *J* = 0.6 Hz, Ar), 5.05 (m, 1H, =CH), 4.51 (m, 2H, $=CH_2$), 4.45 (m, 2H, NCH_2), 2.23 (s, 3H, Me), 2.18 (s, 3H, Me); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 208.5, 141.4, 137.8, 136.0, 130.5, 129.9, 129.1 (Ar, 2CH), 129.0 (Ar, 2CH), 128.5, 123.1 (Ar, CH), 120.0 (Ar, CH), 109.9 (Ar, CH), 101.3 (Ar, CH), 88.2 (=CH), 77.4 ($=CH_2$), 42.9 (NCH_2), 21.4 (Me), 21.3 (Me); IR ($CHCl_3$, cm^{-1}): ν 2920, 1957, 1474, 1341, 849, 827, 790; HRMS (ES): calcd for $C_{20}H_{19}N$ $[M]^+$: 273.1511; found: 273.1523.

1-(Buta-2,3-dienyl)-5-methoxy-2-(4-methylphenyl)-1*H*-indole 66h. From 142 mg (0.52 mmol) of alkyne **65h**, and after chromatography of the residue using hexanes/ethyl

acetate (20:1) as eluent gave compound **66h** (116 mg, 78%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.39 (d, 2H, *J* = 8.2 Hz, Ar), 7.28 (m, 1H, Ar), 7.26 (m, 2H, Ar), 7.08 (d, 1H, *J* = 2.6 Hz, Ar), 6.88 (m, 1H, Ar), 6.43 (d, 1H, *J* = 0.6 Hz, Ar), 5.27 (m, 1H, =CH), 4.72 (m, 2H, $=CH_2$), 4.66 (m, 2H, NCH_2), 3.86 (s, 3H, OMe), 2.41 (s, 3H, Me); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 208.5, 154.4, 141.9, 137.8, 132.9, 130.4, 129.8, 129.2 (Ar, 2CH), 129.1 (Ar, 2CH), 111.7 (Ar, CH), 111.0 (Ar, CH), 102.1 (Ar, CH), 101.4 (Ar, CH), 88.2 (=CH), 77.3 ($=CH_2$), 55.9 (OMe), 43.0 (NCH_2), 21.3 (Me); IR ($CHCl_3$, cm^{-1}): ν 2932, 1960, 1472, 1367, 852, 830, 784; HRMS (ES): calcd for $C_{20}H_{19}NO$ $[M]^+$: 289.1461; found: 289.1466.

1-(Buta-2,3-dienyl)-5-fluoro-2-(4-methylphenyl)-1*H*-indole 66i. From 80 mg (0.30 mmol) of alkyne **65i**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **66i** (69 mg, 83%) as a colorless solid; mp 106–107 °C (*n*-hexane/ethyl acetate); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.42 (d, 2H, *J* = 8.0 Hz, Ar), 7.28 (m, 4H, Ar), 6.98 (dd, 1H, *J* = 9.0, 2.6 Hz, Ar), 6.48 (s, 1H, Ar), 5.30 (m, 1H, =CH), 4.77 (m, 2H, $=CH_2$), 4.70 (m, 2H, NCH_2), 2.44 (s, 3H, Me); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 208.5, 159.7, 156.6, 142.9, 138.2, 134.2, 130.5, 129.5 (Ar, 2CH), 129.3 (Ar, 2CH), 110.8 (Ar, CH), 109.6 (Ar, CH), 105.3 (Ar, CH), 101.7 (Ar, CH), 88.0 (=CH), 77.5 ($=CH_2$), 43.0 (NCH_2), 21.3 (Me); IR ($CHCl_3$, cm^{-1}): ν 2954, 1952, 1476, 1376, 846, 823, 776; HRMS (ES): calcd for $C_{19}H_{16}FN$ $[M]^+$: 277.1261; found: 277.1260.

1-(Buta-2,3-dienyl)-5-nitro-2-phenyl-1*H*-indole 66j. From 129 mg (0.47 mmol) of alkyne **65j**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **66j** (93 mg, 68%) as a colorless solid; mp 121–122 °C (*n*-hexane/ethyl acetate); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 8.59 (d, 1H, *J* = 2.2 Hz, Ar), 8.15 (dd, 1H, *J* = 9.1, 2.2 Hz, Ar), 7.51 (m, 5H, Ar), 7.42 (d, 1H, *J* = 9.1 Hz, Ar), 6.71 (s, 1H, Ar), 5.31 (m, 1H, =CH), 4.76 (m, 4H, $=CH_2 + NCH_2$); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 208.5, 144.5, 142.0, 140.4, 131.4, 129.3 (Ar, 2CH), 128.9 (Ar, CH), 128.8 (Ar, 2CH), 127.3, 117.6 (Ar, CH), 117.3 (Ar, CH), 110.1 (Ar, CH), 104.1 (Ar, CH), 87.6 (=CH), 78.1 ($=CH_2$), 43.0 (NCH_2); IR ($CHCl_3$, cm^{-1}): ν 2970, 1947, 1475, 1387, 838, 808, 753; HRMS (ES): calcd for $C_{18}H_{14}N_2O_2$ $[M]^+$: 290.1049; found: 290.1053.

1-(Buta-2,3-dienyl)-2-phenyl-1*H*-indole-5-carbonitrile 66k. From 80 mg (0.31 mmol) of alkyne **65k**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **66k** (61 mg, 72%) as a colorless solid; mp 113–114 °C (*n*-hexane/ethyl acetate); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.97 (s, 1H, Ar), 7.50 (m, 7H, Ar), 6.61 (s, 1H, Ar), 5.30 (qu, 1H, *J* = 6.6 Hz, =CH), 4.75 (m, 4H, $=CH_2 + NCH_2$); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 208.4, 143.5, 139.1, 131.5, 129.3 (Ar, 2CH), 128.7 (Ar, CH), 128.7 (Ar, 2CH), 127.8, 125.8 (Ar, CH), 124.5 (Ar, CH), 120.8, 111.0 (Ar, CH), 102.9, 102.6 (Ar, CH), 87.6 (=CH), 78.0 ($=CH_2$), 42.9 (NCH_2); IR ($CHCl_3$, cm^{-1}): ν 2959, 1956, 1470, 1350, 840, 813, 756; HRMS (ES): calcd for $C_{19}H_{14}N_2$ $[M]^+$: 270.1151; found: 270.1157.

1-(Buta-2,3-dienyl)-2-methyl-1*H*-indole 66l. From 350 mg (2.12 mmol) of alkyne **65l**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **66l** (303 mg, 78%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.44 (d, 1H, *J* = 7.5 Hz), 7.20 (d, 1H, *J* = 8.0 Hz), 7.06 (td, 1H, *J* = 6.7 Hz, 1.0 Hz), 6.99 (t, 1H, *J* = 7.0 Hz), 6.12 (br s, 1H), 5.14 (q, 1H, *J* = 6.4 Hz), 4.70 (m, 2H), 4.60 (m, 2H), 2.35 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 208.6, 136.6, 136.3, 128.2, 120.7, 120.5, 119.7, 109.0, 100.2, 87.5, 77.4, 41.8, 12.7; IR ($CHCl_3$, cm^{-1}): ν 1956; HRMS (ES): calcd for $C_{13}H_{13}N$ $[M]^+$: 183.1042; found: 183.1042.

1-(Buta-2,3-dienyl)-2,5-dimethyl-1*H*-indole 66m. From 178 mg (0.97 mmol) of alkyne **65m**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as

eluent gave compound **66m** (100 mg, 52%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.36 (s, 1H, Ar), 7.22 (d, 1H, *J* = 8.3 Hz, Ar), 7.02 (dd, 1H, *J* = 8.2, 1.2 Hz, Ar), 6.05 (s, 1H, Ar), 5.26 (m, 1H, *J* = 6.6 Hz, =CH), 4.83 (m, 2H, $=CH_2$), 4.73 (m, 2H, NCH_2), 2.49 (s, 3H, Me), 2.47 (s, 3H, Me); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 208.5, 136.5, 135.0, 128.5, 128.4, 122.0 (Ar, CH), 119.5 (Ar, CH), 108.7 (Ar, CH), 99.6 (Ar, CH), 87.5 (=CH), 77.4 ($=CH_2$), 41.8 (NCH_2), 21.4 (Me), 12.7 (Me); IR ($CHCl_3$, cm^{-1}): ν 2954, 1956, 1475, 1369, 843, 821, 758; HRMS (ES): calcd for $C_{14}H_{15}N$ [*M*]$^+$: 197.1198; found: 197.1205.

1-(Buta-2,3-dienyl)-5-methoxy-2-methyl-1*H*-indole 66n. From 180 mg (0.90 mmol) of alkyne **65n**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **66n** (151 mg, 79%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.18 (d, 1H, *J* = 8.8 Hz, Ar), 7.02 (d, 1H, *J* = 2.5 Hz, Ar), 6.81 (dd, 1H, *J* = 8.8, 2.5 Hz, Ar), 6.19 (s, 1H, Ar), 5.23 (qu, 1H, *J* = 6.5 Hz, =CH), 4.80 (m, 2H, $=CH_2$), 4.66 (m, 2H, NCH_2), 3.86 (s, 3H, OMe), 2.43 (d, 3H, *J* = 0.6 Hz, Me); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 208.5, 153.9, 136.9, 131.8, 128.5, 110.2 (Ar, CH), 109.6 (Ar, CH), 101.9 (Ar, CH), 99.9 (Ar, CH), 87.5 (=CH), 77.0 ($=CH_2$), 55.9 (OMe), 41.9 (NCH_2), 12.7 (Me); IR ($CHCl_3$, cm^{-1}): ν 2932, 1484, 1227, 1202, 847; HRMS (ES): calcd for $C_{14}H_{15}NO$ [*M*]$^+$: 213.1148; found: 213.1146.

1-(Buta-2,3-dienyl)-5-chloro-2-methyl-1*H*-indole 66o. From 355 mg (1.74 mmol) of alkyne **65o**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **66o** (327 mg, 86%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.48 (d, 1H, *J* = 1.9 Hz Ar), 7.19 (d, 1H, *J* = 8.8 Hz, Ar), 7.09 (dd, 1H, *J* = 8.6, 2.0 Hz, Ar), 6.20 (s, 1H, Ar), 5.22 (qu, 1H, *J* = 6.5 Hz, =CH), 4.79 (m, 2H, $=CH_2$), 4.66 (m, 2H, NCH_2), 2.44 (s, 3H, Me); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 208.5, 137.8, 135.0, 129.1, 125.0, 120.7 (Ar, CH), 119.1 (Ar, CH), 109.9 (Ar, CH), 99.9 (Ar, CH), 87.2 (=CH), 77.4 ($=CH_2$), 41.9 (NCH_2), 12.7 (Me); IR ($CHCl_3$, cm^{-1}): ν 2953, 1954, 1474, 1360, 842, 810, 782; HRMS (ES): calcd for $C_{13}H_{12}NCl$ [*M*]$^+$: 217.0652; found: 217.0657.

1-(Buta-2,3-dienyl)-5-bromo-2-methyl-1*H*-indole 66p. From 327 mg (1.32 mmol) of alkyne **65p**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **66p** (301 mg, 87%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.64 (d, 1H, *J* = 1.7Hz, Ar), 7.22 (dd, 1H, *J* = 8.6, 1.8 Hz, Ar), 7.15 (d, 1H, *J* = 8.6 Hz, Ar), 6.20 (s, 1H, Ar), 5.21 (qu, 1H, *J* = 6.4 Hz, =CH), 4.79 (m, 2H, $=CH_2$), 4.66 (m, 2H, NCH_2), 2.43 (s, 3H, Me); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 208.5, 137.7, 135.3, 129.8, 123.2 (Ar, CH), 122.1 (Ar, CH), 112.6, 110.4 (Ar, CH), 99.9 (Ar, CH), 87.2 (=CH), 77.4 ($=CH_2$), 41.9 (NCH_2), 12.6 (Me); IR ($CHCl_3$, cm^{-1}): ν 2924, 1480, 1218, 1200, 850; HRMS (ES): calcd for $C_{13}H_{12}BrN$ [*M*]$^+$: 261.0147; found: 261.0146.

1-(Buta-2,3-dienyl)-2-methyl-5-nitro-1*H*-indole 66q. From 380 mg (1.77 mmol) of alkyne **65q**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound **66q** (289 mg, 72%) as a colorless solid; mp 96–97 °C (*n*-hexane/ethyl acetate); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 8.45 (d, 1H, *J* = 2.2 Hz, Ar), 8.05 (dd, 1H, *J* = 9.0, 2.2 Hz, Ar), 7.27 (d, 1H, *J* = 9.1 Hz, Ar), 6.41 (s, 1H, Ar), 5.26 (m, 1H, *J* = 6.0 Hz, =CH), 4.78 (m, 2H, $=CH_2$), 4.72 (dt, 2H, *J* = 6.0, 2.9 Hz, NCH_2), 2.47 (d, 3H *J* = 0.5 Hz, Me); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 208.4, 141.5, 140.0, 139.6, 127.3, 116.7 (Ar, CH), 116.4 (Ar, CH), 108.7 (Ar, CH), 102.6 (Ar, CH), 86.9 (=CH), 77.9 ($=CH_2$), 42.1 (NCH_2), 12.8 (Me); IR ($CHCl_3$, cm^{-1}): ν 2968, 1967, 1430, 1348, 832; HRMS (ES): calcd for $C_{13}H_{12}N_2O_2$ [*M*]$^+$: 228.0893; found: 228.0904.

Reaction of 1-Allenyl-2-phenyl-indole 66a with Selectfluor. From 50 mg (0.20 mmol) of aminoallene **66a**, and after chromatography of the residue using hexanes/ethyl

acetate (5:1) as eluent, 11 mg (20%) of the less polar compound **67a** and 4 mg (8%) of the more polar compound **68a** were obtained.

1-(Buta-2,3-dienyl)-3-fluoro-2-phenyl-1H-indole 68a. Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.57 (d, 1H, *J* = 7.7 Hz), 7.38 (m, 6H), 7.14 (m, 2H), 5.16 (q, 1H, *J* = 6.0 Hz), 4.65 (m, 2H), 4.59 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –175.4 (s, 1F); HRMS (ES): calcd for $C_{18}H_{14}FN$ [*M*]$^{+}$: 263.1104; found: 263.1118.

General Procedure for the Metal-Catalyzed Reaction of *N*-Allenyl-2-aryl Indoles 66a–i and Selectfluor. Synthesis of 2-(Allenyl)-2-aryl-3,3-difluoroindolines 67a–i. $Fe(OTf)_3$ or $[(Ph_3P)AuNTf_2]$ (0.05 mmol), Selectfluor (2.0 mmol), and $NaHCO_3$ (2.0 mmol) were sequentially added to a stirred solution of the corresponding *N*-allenyl indole **66** (1.0 mmol) in acetonitrile (10 mL) under argon atmosphere. The resulting mixture was stirred at room temperature until disappearance of the starting material (TLC, typically 1 h). After filtration through a pad of Celite, water (5 mL) was added before being extracted with ethyl acetate (3 x 15 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave adducts **67**.

2-(Allenyl)-2-phenyl-3,3-difluoroindoline 67a. From 235 mg (0.96 mmol) of *N*-allenyl indole **66a**, and after chromatography of the residue using hexanes/ethyl acetate (15:1) as eluent gave compound **67a** (227 mg, 83%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.56 (m, 2H), 7.42 (m, 5H), 6.58 (t, 1H, *J* = 7.4 Hz), 6.76 (d, 1H, *J* = 8.0 Hz), 5.18 (q, 1H, *J* = 6.6 Hz), 4.80 (m, 2H), 3.78 (m, 1H), 3.68 (m, 1H), 3.18 (d, 1H, J = 4.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 209.0, 150.2, 134.8, 134.9, 133.4, 129.1 (2C), 128.2, 127.7, 126.3, 124.5, 119.5, 119.0, 108.6, 96.4 (t, *J* = 89.1 Hz), 87.9, 76.7, 42.3; ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –98.44 (d, 1H, *J* = 317.6 Hz), –110.6 (d, 1F, *J* = 317.6 Hz); IR ($CHCl_3$, cm^{-1}): ν 3525, 1955, 1157, 1133; HRMS (ES): calcd for $C_{18}H_{15}F_2N$ [*M*]$^{+}$: 283.1167; found: 283.1183.

2-(Allenyl)-2-(4-chlorophenyl)-3,3-difluoroindoline 67b. From 43 mg (0.15 mmol) of *N*-allenyl indole **66b**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **67b** (32 mg, 66%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.42 (d, 2H, *J* = 8.6 Hz), 7.34 (m, 2H), 7.28 (d, 2H, *J* = 8.8 Hz), 6.81 (t, 1H, *J* = 7.4 Hz), 6.66 (d, 1H, *J* = 8.1 Hz), 5.07 (q, 1H, *J* = 6.6 Hz), 4.71 (m, 2H), 3.68 (m, 1H), 3.55 (m, 1H), 3.09 (d, 1H, *J* = 4.0 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 209.0, 150.0, 135.2, 133.5 (2C), 129.2 (2C), 128.4 (2C), 126.2, 124.5, 122.8, 119.2, 108.8, 95.9 (t, *J* = 89.1 Hz), 87.8, 76.9, 42.2; ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –97.7 (d, 1F, *J* = 263.2 Hz), –110.2 (d, 1F, *J* = 268.1 Hz); IR ($CHCl_3$, cm^{-1}): ν 3525, 1953, 1155, 1135; HRMS (ES): calcd for $C_{18}H_{14}ClF_2N$ [*M*]$^{+}$: 317.0777; found: 317.0792.

2-(Allenyl)-2-(4-fluorophenyl)-3,3-difluoroindoline 67c. From 70 mg (0.27 mmol) of *N*-allenyl indole **66c**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **67c** (32 mg, 40%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.42 (m, 2H), 7.31 (dd, 1H, J = 6.0 Hz, J = 1.5 Hz), 7.13 (m, 1H), 6.74 (t, 2H, *J* = 8.9 Hz), 6.61 (t, 1H, *J* = 7.4 Hz), 6.56 (d, 1H, *J* = 8.0 Hz), 4.89 (q, 1H, *J* = 6.4 Hz), 4.51 (m, 2H), 3.48 (m, 1H), 3.35 (m, 1H), 2.61 (d, 1H, *J* = 3.5 Hz); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 209.8, 165.3, 162.0, 133.4, 130.3, 130.2, 127.0, 126.6, 125.9, 124.7, 119.4, 115.4, 115.1, 109.0, 96.3, 88.3, 76.5, 42.2; ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –95.5 (d, 1F, *J* = 263.2 Hz), –111.6 (d, 1F, *J* = 263.3 Hz), –113.1 (s, 1F); IR ($CHCl_3$, cm^{-1}): ν 3524, 1954, 1160, 1130; HRMS (ES): calcd for $C_{18}H_{14}F_3N$ [*M*]$^{+}$: 301.1072; found: 301.1089.

2-(Allenyl)-2-(4-methylphenyl)-3,3-difluoroindoline 67d. From 96 mg (0.37 mmol) of *N*-allenyl indole **66d**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **67d** (52 mg, 48%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.68 (d, 2H, *J* = 8.2 Hz); 7.47 (dd, 1H, *J* = 8.0, 1.3 Hz), 7.07 (m, 3H), 6.75 (m, 2H), 5.08 (m, 1H), 4.65 (m, 2H), 3.67 (m, 2H), 2.18 (s, 3H); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 206.8, 136.6, 131.0, 130.2, 129.2 (2C), 128.3 (2C), 125.5, 124.6, 123.9, 122.4, 119.9, 116.8, 106.6, 86.2, 74.1, 40.1, 18.7; ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –96.2 (d, 1F, *J* = 263.2 Hz), –111.3 (d, 1F, *J* = 263.2 Hz); IR ($CHCl_3$, cm^{-1}): ν 3525, 1952, 1161, 1136; HRMS (ES): calcd for $C_{19}H_{17}F_2N$ [*M*]$^{+}$: 297.1323; found: 297.1322.

2-(Allenyl)-2-(4-*tert*-butylphenyl)-3,3-difluoroindoline 67e. From 48 mg (0.16 mmol) of *N*-allenyl indole **66e**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **67e** (23 mg, 43%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.54 (d, 2H, *J* = 8.3 Hz), 7.39 (d, 1H, *J* = 8.6 Hz); 7.23 (dd, 1H, *J* = 7.6, 1.6 Hz), 7.16 (d, 2H, *J* = 8.8 Hz); 6.52 (m, 2H), 4.86 (m, 1H), 4.43 (m, 2H), 3.43 (m, 2H), 1.06 (s, 9H); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 207.7, 150.7, 142.3, 132.0, 131.1, 127.5, 126.9 (2C), 126.6 (2C), 126.0, 125.1, 124.3 (2C), 124.2, 123.4, 117.8, 107.5, 87.2, 75.1, 41.1, 29.9; ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –96.0 (d, 1F, *J* = 263.2 Hz), –110.9 (d, 1F, *J* = 263.2 Hz); IR ($CHCl_3$, cm^{-1}): ν 3528, 1954, 1154, 1134; HRMS (ES): calcd for $C_{22}H_{23}F_2N$ [*M*]$^{+}$: 339.1793; found: 339.1790.

2-(Allenyl)-2-(naphthalen-2-yl)-3,3-difluoroindoline 67f. From 60 mg (0.25 mmol) of *N*-allenyl indole **66f**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **67f** (45 mg, 55%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 8.19 (s, 1H), 7.49 (m, 4H), 7.27 (dd, 1H, *J* = 7.9, 1.4 Hz), 7.12 (m, 3H), 6.53 (d, 2H, *J* = 7.7 Hz); 4.86 (m, 1H), 4.42 (m, 2H), 3.42 (m, 2H); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 209.2, 134.2, 133.6, 133.5, 133.1, 128.9, 128.3, 128.2 (2C), 127.9, 126.8, 126.4, 125.6 (2C), 124.9, 123.8, 120.5, 119.4, 109.0, 88.5, 76.5, 42.4; ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –95.4 (d, 1F, *J* = 268.1 Hz), –110.5 (d, 1F, *J* = 263.2 Hz); IR ($CHCl_3$, cm^{-1}): ν 3525, 1951, 1152, 1132; HRMS (ES): calcd for $C_{22}H_{17}F_2N$ [*M*]$^{+}$: 333.1323; found: 333.1337.

5-Methyl-2-(allenyl)-2-(4-methylphenyl)-3,3-difluoroindoline 67g. From 49 mg (0.18 mmol) of *N*-allenyl indole **66g**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **67g** (29 mg, 52%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.59 (d, 2H, *J* = 8.2 Hz, Ar), 6.97 (d, 3H, *J* = 7.9 Hz, Ar), 6.85 (s, 1H, Ar), 6.66 (m, 1H, Ar), 5.22 (m, 1H, *J* = 6.4 Hz, =CH), 4.53 (m, 2H, =CH_2), 3.97 (m, 1H, CH*H*), 3.71 (m, 1H, C*H*H), 2.77 (d, 1H, *J* = 3.2 Hz, NH), 2.06 (s, 3H, Me), 1.84 (s, 3H, Me); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 209.1, 139.1 (Ar, CH), 138.9, 133.9, 132.8, 131.1, 129.3 (Ar, 2CH), 128.4 (Ar, 2CH), 125.3 (Ar, CH), 121.0, 120.7, 109.0 (Ar, CH), 97.1, 88.8 (=CH), 76.5 (=CH_2), 42.7 (CH_2), 21.1(Me), 20.5 (Me); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –94.7 (d, 1F, *J* = 268.1 Hz), –111.7 (d, 1F, *J* = 263.2 Hz); IR ($CHCl_3$, cm^{-1}): ν 2925, 1713, 1501, 1328, 1272, 1095, 857, 823; HRMS (ES): calcd for $C_{20}H_{19}F_2N$ [*M*]$^{+}$: 311.1480; found: 311.1487.

5-Methoxy-2-(allenyl)-2-(4-methylphenyl)-3,3-difluoroindoline 67h. From 56 mg (0.19 mmol) of *N*-allenyl indole **66h**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **67h** (26 mg, 42%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.63 (d, 2H, *J* = 8.2 Hz, Ar), 7.03 (m, 1H, Ar), 6.99 (d, 2H, *J* = 8.0 Hz, Ar), 6.92 (m, 1H, Ar), 6.58 (d, 1H, *J* = 8.6 Hz, Ar), 5.03 (m, 1H, *J* = 6.3 Hz, =CH), 4.55 (m, 2H, =CH_2), 3.55 (m, 1H, CH*H*), 3.47 (m, 1H, C*H*H), 3.23 (s, 3H, OMe), 2.71 (d, 1H, *J* = 3.4 Hz, NH), 2.07(s, 3H, Me); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 209.1,

154.1, 145.0, 139.0, 132.7, 129.2 (Ar, 4CH), 128.9, 120.5 (Ar, CH), 113.0, 110.4 (Ar, CH), 109.4 (Ar, CH), 97.3, 88.9 (=CH), 76.4 (=CH_2), 55.5 (OMe), 43.0 (CH_2), 21.1(Me); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –96.0 (d, 1F, *J* = 263.3 Hz), –113.1 (d, 1F, *J* = 268.1 Hz); IR ($CHCl_3$, cm^{-1}): ν 2926, 1706, 1495, 1276, 1073, 825; HRMS (ES): calcd for $C_{20}H_{19}F_2NO$ $[M]^+$: 327.1429; found: 327.1434.

5-Fluoro-2-(allenyl)-2-(4-methylphenyl)-3,3-difluoroindoline 67i. From 32 mg (0.12 mmol) of *N*-allenyl indole **66i**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **67i** (16 mg, 44%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.52 (d, 2H, *J* = 8.2 Hz, Ar), 6.99 (m, 1H, Ar), 6.97 (d, 2H, *J* = 7.9 Hz, Ar), 6.81 (m, 1H, Ar), 6.33 (m, 1H, Ar), 4.92 (m, 1H, *J* = 6.4 Hz, =CH), 4.51 (m, 2H, =CH_2), 3.51 (m, 1H, CH*H*), 3.45 (m, 1H, C*H*H), 2.63 (d, 1H, *J* = 3.1 Hz, NH), 2.06 (s, 3H, Me); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 209.1, 139.2 (2C), 132.20, 132.16, 129.3 (Ar, 2CH), 128.2 (Ar, 2CH), 127.2, 126.6, 119.9 (d, *J* = 93.8 Hz, Ar, CH), 112.0 (d, *J* = 98.2 Hz, Ar, CH), 109.8 (d, *J* = 28.4 Hz, Ar, CH), 97.3 (dd, *J* = 124.4, 87.3 Hz, Ar, C), 87.3 (=CH), 76.6 (=CH_2), 42.7 (CH_2), 21.1(Me); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –96.2 (d, 1F, *J* = 268.1 Hz), –113.3 (d, 1F, *J* = 268.2 Hz); IR ($CHCl_3$, cm^{-1}): ν 2924, 1700, 1492, 1266, 1187, 843, 814; HRMS (ES): calcd for $C_{19}H_{16}F_3N$ $[M]^+$: 315.1229; found: 315.1243.

2-(Buta-2,3-dienyl)-3,3-difluoro-5-nitro-2-phenylindoline 67j. From 47 mg (0.16 mmol) of *N*-allenyl indole **66j**, 49 mg (92%) of compound **67j** was obtained as a pale yellow solid; mp 123–124 °C (*n*-hexane/ethyl acetate); ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 8.15 (d, 1H, *J* = 1.8 Hz, Ar), 7.98 (dd, 1H, *J* =8.9, 2.3 Hz, Ar), 7.41 (m, 2H, Ar), 7.12 (m, 3H, Ar), 6.06 (d, 1H, *J* = 9.1 Hz, Ar), 4.74 (qu, 1H, *J* = 6.4 Hz, =CH), 4.48 (m, 2H, =CH_2), 3.30 (m, 2H, CH_2), 3.03 (br s, 1H, NH); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 209.1, 154.4 (t, *J* = 24.0 Hz, C), 140.4, 134.2, 130.2, 129.8 (Ar, 2CH), 128.9 (Ar, CH), 127.9 (Ar, 2CH), 125.0, 121.7 (Ar, CH), 120.0 (t, *J* = 102.5 Hz, C), 107.3 (Ar, CH), 97.1 (dd, *J* = 124.3, 89.4 Hz, Ar, C), 87.3 (=CH), 77.1 (=CH_2), 41.7(CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –97.9 (d, 1F, *J* = 251.1 Hz), –108.5 (d, 1F, *J* = 252.3 Hz); IR ($CHCl_3$, cm^{-1}): ν 2930, 1622, 1507, 1328, 1269, 1099, 758, 707; HRMS (ES): calcd for $C_{18}H_{14}F_2N_2O_2$ $[M]^+$: 328.1017; found: 328.1038.

2-(Buta-2,3-dienyl)-3,3-difluoro-2-phenylindoline-5-carbonitrile 67k. From 30 mg (0.11 mmol) of *N*-allenyl indole **66k**, 33 mg (97%) of compound **67k** was obtained as a colorless solid; mp 118–119 °C (*n*-hexane/ethyl acetate); ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.48 (d, 2H, *J* = 7.7 Hz, Ar), 7.11 (m, 3H, Ar), 7.03 (s, 1H, Ar), 7.00 (d, 1H, *J* = 9.3 Hz, Ar), 6.13 (d, 1H, *J* = 8.3 Hz, Ar), 4.79 (m, 1H, *J* = 6.4 Hz, =CH), 4.48 (m, 2H, =CH_2), 3.33 (m, 3H, CH_2 + NH); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 209.1, 152.9 (t, *J* = 26.2 Hz, Ar, C), 137.7 (Ar, CH), 134.5 (d, *J* = 10.9 Hz, Ar, C), 129.6 (Ar, CH), 128.9 (Ar, CH), 128.6 (Ar, 2CH), 128.3 (Ar, CH), 127.9 (Ar, 2CH), 125.5 (t, *J* = 113.5 Hz, Ar, C), 120.8 (t, *J* = 102.5 Hz, Ar, C), 119.0, 108.6 (Ar, CH), 101.8, 96.7 (dd, *J* = 124.3, 89.4 Hz, Ar, C), 87.4 (=CH), 76.9 (=CH_2), 41.8 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –96.9 (d, 1F, *J* = 251.9 Hz), –109.4 (d, 1F, *J* = 251.9 Hz); IR ($CHCl_3$, cm^{-1}): ν 2858, 2224, 1626, 1499, 1178, 1097, 856, 735; HRMS (ES): calcd for $C_{19}H_{14}F_2N_2$ $[M]^+$: 308.1119; found: 308.1112.

Procedure for the Iron-Catalyzed Reaction of 1-(Allenyl)-2-methyl-1*H*-indoles 66l–q and Selectfluor. Synthesis of 2-(Allenyl)-3,3-difluoro-2-methyl indolines 67l, 67m, and 67o-q. $Fe(OTf)_3$ (0.0715 mmol), Selectfluor (2.86 mmol), and $NaHCO_3$ (2.86 mmol) were sequentially added at 0 ^{o}C to a stirred solution of the appropriate *N*-allenyl-2-methyl indole **66** (1.43 mmol) in acetonitrile (14 mL) under argon atmosphere. The resulting mixture was stirred at 0 ^{o}C until disappearance of the starting material (TLC, 5 min). After filtration through a pad of Celite, water (7 mL) was added before being extracted with ethyl acetate (3 x 20 mL). The organic layer was dried ($MgSO_4$) and concentrated

under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave adducts **67**.

2-(Buta-2,3-dienyl)-2-methyl-3,3-difluoroindoline 67l. From 88 mg (0.48 mmol) of aminoallene **66l**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **67l** (50 mg, 47%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.35 (d, 1H, *J* = 7.4 Hz, Ar), 7.07 (t, 1H, *J* = 7.6 Hz, Ar), 6.56 (d, 1H, *J* = 8.0 Hz, Ar), 6.38 (d, 1H, *J* = 8.0 Hz, Ar), 4.91 (m, 1H, *J* = 6.5 Hz, =CH), 4.52 (m, 2H, =CH_2), 3.50 (m, 2H, CH_2), 2.11 (br s, 1H, NH), 1.32 (d, 3H, *J* = 2.9 Hz, Me); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 209.0, 149.4, 133.3 (Ar, CH), 124.5 (Ar, CH), 123.8, 120.1, 118.7 (Ar, CH), 108.4 (Ar, CH), 93.4 (dd, *J* = 115.7, 93.8 Hz, Ar, C), 88.4 (=CH), 76.5 (=CH_2), 40.6 (CH_2), 18.2 (d, *J* = 30.6 Hz, Me); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –107.7 (d, 1F, *J* = 268.2 Hz), –108.9 (d, 1F, *J* = 268.2 Hz); IR ($CHCl_3$, cm^{-1}): ν 2930, 1623, 1480, 1249, 1065, 843, 814; HRMS (ES): calcd for $C_{13}H_{13}F_2N$ [*M*]$^{+}$: 221.1010; found: 221.1021.

2-(Buta-2,3-dienyl)-3,3-difluoro-5-methyl-2-methylindoline 67m. From 40 mg (0.20 mmol) of aminoallene **66m**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **67m** (23 mg, 48%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.16 (s, 1H, Ar), 6.92 (d, 1H, *J* = 8.5 Hz, Ar), 6.37 (d, 1H, *J* = 8.0 Hz, Ar), 4.96 (m, 1H, *J* = 6.5 Hz, =CH), 4.55 (m, 2H, =CH_2), 3.53 (m, 2H, CH_2), 2.01 (s, 3H, Me), 1.35 (d, 3H, *J* = 3.7 Hz, Me); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 209.0 147.5 (t, *J* = 26.1 Hz, Ar, C), 133.8 (Ar, CH), 124.9 (Ar, CH), 123.9, 120.3 (t, *J* = 106.9 Hz, Ar, C), 108.5 (Ar, CH), 93.7 (dd, *J* = 115.6, 93.8 Hz, Ar, C), 88.6 (=CH), 76.4 (=CH_2), 40.9 (CH_2), 20.5 (Me), 18.1 (d, *J* = 30.5 Hz, Me); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –107.8 (d, 1F, *J* = 267.9 Hz), –109.3 (d, 1F, *J* = 268.2 Hz); IR ($CHCl_3$, cm^{-1}): ν 2937, 1713, 1470, 1245, 1157, 823; HRMS (ES): calcd for $C_{14}H_{15}F_2N_2$ [*M*]$^{+}$: 235.1167; found: 235.1189.

2-(Buta-2,3-dienyl)-5-chloro-3,3-difluoro-2-methylindoline 67o. From 67 mg (0.31 mmol) of aminoallene **66o**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **67o** (33 mg, 41%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.29 (d, 1H, *J* = 1.7 Hz, Ar), 7.02 (d, 1H, *J* = 8.6 Hz, Ar), 6.06 (d, 1H, *J* = 8.5 Hz, Ar), 4.81 (m, 1H, *J* = 6.4 Hz, =CH), 4.49 (m, 2H, =CH_2), 3.36 (m, 2H, CH_2), 2.02 (br s, 1H, NH), 1.25 (dd, 3H, *J* = 3.6, 0.9 Hz, Me); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 208.9, 147.8 (t, *J* = 25.0 Hz, Ar, C), 133.2 (Ar, CH), 126.2, 124.7 (Ar, CH), 123.1 (d, *J* = 150.5 Hz, Ar, C), 121.2 (t, *J* = 100.4 Hz, Ar, C), 109.5 (Ar, CH), 93.5 (dd, *J* = 111.2, 93.8 Hz, Ar, C), 87.9 (=CH), 76.8 (=CH_2), 40.4 (CH_2), 18.2 (dd, *J* = 28.3, 6.5 Hz, Me); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –108.0 (d, 1F, *J* = 268.2 Hz), –109.2 (d, 1F, *J* = 268.2 Hz); IR ($CHCl_3$, cm^{-1}): ν 2926, 1614, 1483, 1256, 1069, 851, 808; HRMS (ES): calcd for $C_{13}H_{12}NClF_2$ [*M*]$^{+}$: 255.0620; found: 255.0637.

2-(Buta-2,3-dienyl)-5-bromo-3,3-difluoro-2-methylindoline 67p. From 80 mg (0.31 mmol) of aminoallene **66p**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **67p** (38 mg, 42%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.44 (dd, 1H, *J* = 3.3, 1.6 Hz, Ar), 7.14 (m, 1H, Ar), 6.02 (d, 1H, *J* = 8.5 Hz, Ar), 4.80 (m, 1H, *J* = 6.4 Hz, =CH), 4.49 (dt, 2H, *J* = 6.3, 3.0 Hz, NCH_2), 3.36 (m, 2H, CH_2), 2.11 (br s, 1H, NH), 1.23 (dd, 3H, *J* = 3.5, 0.9 Hz, Me); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 208.9, 148.2 (t, *J* = 26.0 Hz, Ar, C), 136.0 (Ar, CH), 126.1, 122.8, 121.9 (t, *J* = 100.4 Hz, Ar, C), 110.0 (Ar, CH), 93.4 (dd, *J* = 113.5, 94.1 Hz, Ar, C), 87.9 (=CH), 76.8 (=CH_2), 40.3 (CH_2), 18.2 (d, *J* = 28.8 Hz, Me); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –107.9 (d, 1F, *J* = 251.8 Hz), –109.1 (d, 1F, *J* = 251.6 Hz); IR ($CHCl_3$, cm^{-1}): ν 2924, 1610, 1472, 1254, 1084, 853, 802; HRMS (ES): calcd for $C_{13}H_{12}NBrF_2$ [*M*]$^{+}$: 299.0115; found: 299.0137.

2-(Buta-2,3-dienyl)-3,3-difluoro-5-nitro-2-methylindoline 67q. From 73 mg (0.32 mmol) of aminoallene **66q**, and after chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave compound **67q** (49 mg, 57%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 8.18 (dd, 1H, *J* = 3.8, 1.8 Hz, Ar), 7.91 (dd, 1H, *J* = 9.0, 2.3 Hz, Ar), 5.85 (dd, 1H, *J* = 9.0, 1.2 Hz, Ar), 4.72 (m, 1H, *J* = 6.5 Hz, =CH), 4.49 (m, 2H, =CH_2), 3.35 (m, 2H, CH_2), 2.41 (br s, 1H, NH), 1.22 (d, 3H, *J* = 4.0 Hz, Me); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 208.9, 153.0 (t, *J* = 24.0 Hz, Ar, C), 139.7, 130.2 (Ar, CH), 125.1, 121.5 (Ar, CH), 119.5 (t, *J* = 103.4 Hz, Ar, C), 106.8 (Ar, CH), 93.7 (dd, *J* = 119.0, 91.2 Hz, Ar, C), 87.1 (=CH), 77.4 (=CH_2), 39.8 (CH_2), 18.6(d, *J* = 28.8 Hz, Me); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –106.7 (d, 1F, *J* = 252.9 Hz), –108.4 (d, 1F, *J* = 252.9 Hz); IR ($CHCl_3$, cm^{-1}): ν 2932, 1702, 1490, 1242, 1150, 830; HRMS (ES): calcd for $C_{13}H_{12}N_2O_2F_2$ [*M*]$^{+}$: 266.0861; found: 266.0851.

Procedure for the Iron-Catalyzed Reaction of 1-(Allenyl)-2-methyl-1*H*-indoles 66l–q and Selectfluor. Synthesis of 2-(Allenyl)-3,3-difluoro-2-(fluoromethyl)indolines 69l, 69m, and 69o-q. $Fe(OTf)_3$ (0.0715 mmol), Selectfluor (5.00 mmol), and $NaHCO_3$ (5.00 mmol) were sequentially added to a stirred solution of the appropriate *N*-allenyl-2-methyl indole **66** (1.43 mmol) in acetonitrile (14 mL) under argon atmosphere. The resulting mixture was stirred at room temperature until disappearance of the starting material (TLC, 5 min). After filtration through a pad of Celite, water (7 mL) was added before being extracted with ethyl acetate (3 x 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave adducts **69**.

2-(Buta-2,3-dienyl)-3,3-difluoro-2-(fluoromethyl)indoline 69l. From 88 mg (0.48 mmol) of aminoallene **66l**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **69l** (55 mg, 48%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.28 (d, 1H, *J* = 7.4, 1.2 Hz, Ar), 7.03 (td, 1H, *J* = 8.2, 1.2 Hz, Ar), 6.53 (t, 1H, *J* = 7.4 Hz, Ar), 6.37 (d, 1H, *J* = 8.2 Hz, Ar), 4.91 (m, 1H, *J* = 6.3Hz, =CH), 4.51 (m, 2H, =CH_2), 4.45 (d, 1H, *J* = 1.5 Hz, CH*H*F), 4.30 (d, 1H, *J* = 1.3 Hz, C*H*HF), 3.61 (m, 1H, CH*H*), 3.46 (m, 1H, C*H*H), 2.62 (br s, 1H, NH); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 208.9, 150.0, 133.5 (Ar, CH), 124.3 (Ar, CH), 123.9, 119.8, 119.1 (Ar, CH), 108.5 (Ar, CH), 91.6 (dd, *J* = 122.2, 87.3 Hz, Ar, C), 88.3 (=CH), 80.4 (dd, *J* = 709.1, 37.1 Hz, Ar, CH_2F), 76.7 (=CH_2), 41.1 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –103.5 (d, 1F, *J* = 273.0 Hz), –107.0 (dd, 1F, *J* = 273.0, 14.6 Hz), –230.5 (d, 1F, *J* = 14.6 Hz); IR ($CHCl_3$, cm^{-1}): ν 2930, 1614, 1480, 1260, 1084, 846, 809; HRMS (ES): calcd for $C_{13}H_{12}NF_3$ [*M*]$^{+}$: 239.0916; found: 239.0922.

2-(Buta-2,3-dienyl)-3,3-difluoro-2-(fluoromethyl)-5-methylindoline 69m. From 46 mg (0.23 mmol) of aminoallene **66m**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **69m** (30 mg, 51%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.11 (s, 1H, Ar), 6.88 (d, 1H, *J* = 7.9 Hz, Ar), 6.35 (d, 1H, *J* = 8.2 Hz, Ar), 4.96 (m, 1H, *J* = 6.6Hz, =CH), 4.52 (m, 2H, =CH_2), 4.49 (d, 1H, *J* = 2.5 Hz, CH*H*F), 4.33 (d, 1H, *J* = 2.5 Hz, C*H*HF), 3.64 (m, 1H, CH*H*), 3.50 (m, 1H, C*H*H), 2.63 (br s, 1H, NH), 1.96 (s, 3H, Me); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 208.9, 148.0 (t, *J* = 26.1 Hz, Ar, C), 145.7, 134.1 (Ar, CH), 124.7 (Ar, CH), 124.0, 120.0, 108.5 (Ar, CH), 91.8, 88.5 (=CH), 80.7 (dd, *J* = 709.1, 39.3 Hz, Ar, C), 76.6 (=CH_2), 41.4 (CH_2), 20.4 (Me); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –103.9 (d, 1F, *J* = 273.0 Hz), –106.6 (dd, 1F, *J* = 273.0, 9.6 Hz), –230.5 (d, 1F, *J* = 9.9 Hz); IR ($CHCl_3$, cm^{-1}): ν 2926, 1708, 1486, 1260, 1157, 828; HRMS (ES): calcd for $C_{14}H_{14}NF_3$ [*M*]$^{+}$: 253.1072; found: 253.1077

2-(Buta-2,3-dienyl)-5-chloro-3,3-difluoro-2-(fluoromethyl)indoline 69o. From 67 mg (0.31 mmol) of aminoallene **66o**, and after chromatography of the residue using

hexanes/ethyl acetate (20:1) as eluent gave compound **69o** (36 mg, 45%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.22 (d, 1H, *J* = 1.9 Hz, Ar), 6.98 (d, 1H, *J* = 8.1 Hz, Ar), 6.05 (d, 1H, *J* = 8.5 Hz, Ar), 4.82 (qu, 1H, *J* = 6.3Hz, =CH), 4.47 (m, 2H, =CH_2), 4.37 (d, 1H, *J* = 2.3 Hz, CH*H*F), 4.21 (d, 1H, *J* = 2.3 Hz, C*H*HF), 3.48 (m, 1H, CH*H*), 3.32 (m, 1H, C*H*H), 2.50 (br s, 1H, NH); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 208.8, 148.4 (t, *J* = 26.1 Hz, Ar, C), 133.5 (Ar, CH), 124.5 (Ar, CH), 124.0, 122.9, 121.1, 109.6 (Ar, CH), 92.1 (dd, *J* = 120.0, 87.3 Hz, Ar, C), 87.8 (=CH), 80.4 (dd, *J* = 709.1, 37.1 Hz, Ar, CH_2F), 76.9 (=CH_2), 40.9 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –103.5 (d, 1F, *J* = 273.0 Hz), –108.0 (dd, 1F, *J* = 273.0, 9.8 Hz), –230.6 (d, 1F, *J* = 9.8 Hz); IR ($CHCl_3$, cm^{-1}): ν 2925, 1620, 1488, 1260, 1080, 853, 811; HRMS (ES): calcd for $C_{13}H_{11}NClF_3$ [*M*]$^{+}$: 273.0526; found: 273.0530.

2-(Buta-2,3-dienyl)-5-bromo-3,3-difluoro-2-(fluoromethyl)indoline 69p. From 76 mg (0.29 mmol) of aminoallene **66p**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **69p** (50 mg, 54%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.38 (d, 1H, *J* = 1.7 Hz, Ar), 7.13 (d, 1H, *J* = 9.8 Hz, Ar), 6.02 (d, 1H, *J* = 8.5 Hz, Ar), 4.85 (m, 1H, *J* = 6.4 Hz, =CH), 4.48 (m, 2H, =CH_2), 4.39 (t, 1H, *J* = 2.55 Hz, CH*H*F), 4.24 (t, 1H, *J* = 2.6 Hz, C*H*HF), 3.52 (m, 1H, CH*H*), 3.34 (m, 1H, C*H*H), 3.02 (br s, 1H, NH); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 208.9, 148.8 (t, *J* = 26.2 Hz, Ar, C), 136.2 (Ar, CH), 128.0 (Ar, CH), 121.7 (t, *J* = 25.1 Hz, Ar, C), 110.5, 110.0 (Ar, CH), 92.0 (dd, *J* = 171.3, 85.5 Hz, Ar, C), 87.8 (=CH), 81.6 (dd, *J* = 709.9, 37.8 Hz, Ar, CH_2F), 76.9 (=CH_2), 40.9(CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –102.2 (d, 1F, *J* = 257.2 Hz), –107.0 (dd, 1F, *J* = 257.4, 9.6 Hz), –229.4 (d, 1F, *J* = 9.2 Hz); IR ($CHCl_3$, cm^{-1}): ν 2923, 1608, 1476, 1256, 1059, 867, 805; HRMS (ES): calcd for $C_{13}H_{11}NBrF_3$ [*M*]$^{+}$: 317.0021; found: 317.0041.

2-(Buta-2,3-dienyl)-3,3-difluoro-5-nitro-2-(fluoromethyl)indoline 69q. From 50 mg (0.22 mmol) of aminoallene **66q**, 57 mg (91%) of compound **69q** was obtained as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 8.16 (dd, 1H, *J* = 3.7, 1.8Hz, Ar), 7.89 (dd, 1H, *J* = 9.0, 2.2 Hz, Ar), 5.89 (d, 1H, *J* = 9.0 Hz, Ar), 4.81 (m, 1H, *J* = 6.5 Hz, =CH), 4.51 (m, 2H, =CH_2), 4.48 (m, 1H, CH*H*F), 4.19 (d, 1H, C*H*HF), 3.51 (m, 1H, CH*H*), 3.35 (m, 1H, C*H*H); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 208.9, 153.7, 140.2, 130.3 (Ar, CH), 121.8, 121.1(Ar, CH), 119.6 (t, *J* = 101.3 Hz, Ar, C), 107.0 (Ar, CH), 92.3 (dd, *J* = 205.5, 84.2 Hz, Ar, C), 86.9 (=CH), 80.0 (dd, *J* = 712.7, 37.3 Hz, Ar, CH_2F), 77.3 (=CH_2), 40.3 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –100.9 (d, 1F, *J* = 258.9 Hz), –110.8 (dd, 1F, *J* = 258.9, 12.5 Hz), –230.0 (d, 1F, *J* = 12.3 Hz); IR ($CHCl_3$, cm^{-1}): ν 2940, 1680, 1474, 1264, 1080, 846, 800; HRMS (ES): calcd for $C_{13}H_{11}N_2O_2F_3$ [*M*]$^{+}$: 284.0767; found: 284.0791

Procedure for the Pd(II)-Catalyzed Cyclization of 2-Allenyl-1*H*-indoles 67 in Presence of Allyl Bromide. Preparation of 7-allyl-9a-(4-substituted)-10,10-difluoro-6,9,9a,10-tetrahydropyrido[1,2-*a*]indoles 75. Palladium(II) chloride (0.004 mmol) was added to a stirred solution of the appropriate β-aminoallene **67** (0.08 mmol) and allyl bromide (0.40 mmol) in *N*,*N*-dimethylformamide (0.5 mL). The reaction was stirred under argon atmosphere until disappearance of the starting material (TLC, 24 h). Water (0.4 mL) was added before being extracted with ethyl acetate (3 x 4 mL). The organic phase was washed with water (2 x 2 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave adducts **75**.

10,10-Difluoro-tetrahydropyrido[1,2-*a*]indole 75a. From 48 mg (0.17 mmol) of β-aminoallene **67a**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **75a** (28 mg, 50%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.66 (d, 2H, *J* = 7.7 Hz, Ar), 6.93 (m, 6H, Ar), 6.73 (d, 1H, *J* = 7.9 Hz, Ar), 5.58 (m, 1H, =CH), 4.92 (m, 2H, =CH_2), 4.88 (dd, 2H, *J* = 11.3, 1.4 Hz, CH_2), 3.38 (dd, 2H, *J* = 11.1, 2.9 Hz, CH_2), 3.37 (s, 2H, CH_2), 2.42 (d, 2H, *J* = 6.3 Hz, CH_2); ^{13}C-NMR (75 MHz,

C_6D_6, 25 °C) δ: 138.4, 135.5, 135.0 (Ar, CH), 134.2, 132.2 (Ar, 2CH), 129.1 (Ar, CH), 128.6 (Ar, 2CH), 128.0 (=CH), 126.5 (=CH), 125.9 (Ar, CH), 124.6 (Ar, CH), 120.0 (Ar, CH), 116.4 (=CH_2), 115.6, 114.9, 62.4 (CH_2), 60.7 (CH_2), 33.4 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –92.6 (s, 2F); IR (C_6D_6, cm^{-1}): ν 2927, 1703, 1499, 1256, 1180, 840, 810; HRMS (ES): calcd for $C_{21}H_{19}F_2N$ [*M*]$^+$: 323.1480; found: 323.1469.

10,10-Difluoro-tetrahydropyrido[1,2-*a*]indole 75b. From 26 mg (0.08 mmol) of β-aminoallene **67b**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **75b** (13 mg, 46%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.87 (d, 1H, *J* = 7.9 Hz), 7.67 (d, 2H, *J* = 8.5 Hz), 7.50 (t, 1H, *J* = 7.5 Hz); 7.37 (t, 1H, *J* = 7.5 Hz), 7.28 (d, 2H, *J* = 8.6 Hz), 7.22 (d, 1H, *J* = 8.0 Hz), 5.76 (m, 1H), 5.25 (br s, 1H), 5.05 (m, 2H), 3.47 (br s, 2H), 3.38 (br s, 2H), 2.72 (d, 2H, *J* = 6.0 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ: 148.9, 138.7, 138.2, 134.6, 133.5, 132.4, 132.3, 131.8, 129.6, 128.5 (2C), 126.2 (2C), 125.2, 124.4, 119.6, 116.6, 78.5, 62.1, 60.6, 33.2; ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –95.5 (d, 1F, *J* = 263.2 Hz), –111.6 (d, 1F, *J* = 263.3 Hz); HRMS (ES): calcd for $C_{21}H_{18}ClF_2N$ [*M*]$^+$: 357.1090; found: 357.1089.

10,10-Difluoro-tetrahydropyrido[1,2-*a*]indole 75l. From 30 mg (0.14 mmol) of β-aminoallene **67l**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **75l** (28 mg, 32%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 °C) δ: 7.71 (d, 2H, *J* = 7.8 Hz, Ar), 7.05 (t, 1H, *J* = 7.3 Hz, Ar), 6.88 (dd, 1H, *J* = 12.4, 7.8 Hz, Ar), 5.62 (m, 1H, =CH), 4.98 (m, 2H, =CH_2), 4.97 (m, 2H, CH_2), 3.60 (dd, 2H, *J* = 19.2, 2.7 Hz, CH_2), 3.59 (m, 2H, CH_2), 2.47 (d, 2H, *J* = 6.0 Hz, CH_2), 2.12 (d, 3H, *J* = 1.2 Hz, Me); ^{13}C-NMR (75 MHz, C_6D_6, 25 °C) δ: 138.9, 135.0 (Ar, CH), 132.3 (=CH), 128.9, 126.9 (=CH), 126.2 (Ar, CH), 125.7 (Ar, CH), 125.1, 124.9, 120.4 (Ar, CH), 116.6 (=CH_2), 63.5 (CH_2), 62.1 (CH_2), 33.4 (CH_2), 23.6 (Me); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –99.7 (s, 2F); IR (C_6D_6, cm^{-1}): ν 2935, 1634, 1474, 1245, 1056, 840; HRMS (ES): calcd for $C_{16}H_{17}F_2N$ [*M*]$^+$: 261.1323; found: 261.1348.

IX.4. Notes and references

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11 Although the isolation of 1-(buta-2,3-dienyl)-3-fluoro-2-phenyl-1*H*-indole **68a** from the uncatalyzed reaction of **66a** outlined in Scheme IX.2 was fortuitous, some information has been gathered in favor of the pathway shown in Scheme IX.6.

12 In order to see if compound **68a** is able to rearrange to **67a** under metal catalysis, reaction of **68a** with a catalytic amount of either $Fe(OTf)_3$ or $[(Ph_3P)AuNTf_2]$ was conducted in the presence of Selectfluor and $NaHCO_3$. The reaction did proceed well to give 3,3-difluoroindoline **67a**. Therefore, we have enough evidence to propose that 3-fluoroindole **68a** is indeed an intermediate.

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X. CAPÍTULO 7

X.1. Metal-Catalyzed Cyclization Reactions of 2,3,4-Trien-1-ols: A joint Experimental-Computational Study

Controlled preparation of tri- and tetrasubstituted furans, as well as carbazoles has been achieved through chemo- and regioselective metal-catalyzed cyclization reactions of cumulenic alcohols. The gold- and palladium-catalyzed cycloisomerization reaction of cumulenols, including indole-tethered 2,3,4-trien-1-ols, was effective as 5-endo-dig oxycyclization by attack of the hydroxy group to the central cumulene double bond to afford trisubstituted furans; whereas their palladium- catalyzed heterocyclization/coupling reactions with 3-bromoprop-1-enes furnished tetrasubstituted furans. By contrast, the palladium-catalyzed cyclization/coupling sequence involving protected indole-tethered 2,3,4-trien-1-ols and 3-bromoprop-1-enes exclusively generated trisubstituted carbazole derivatives. These results could be explained through a selective 6-endo-dig cumulenic hydroarylation, followed by aromatization. Density Functional Theory calculations were carried out to understand this difference in reactivity

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X.2. Article

X.2.1. Introduction

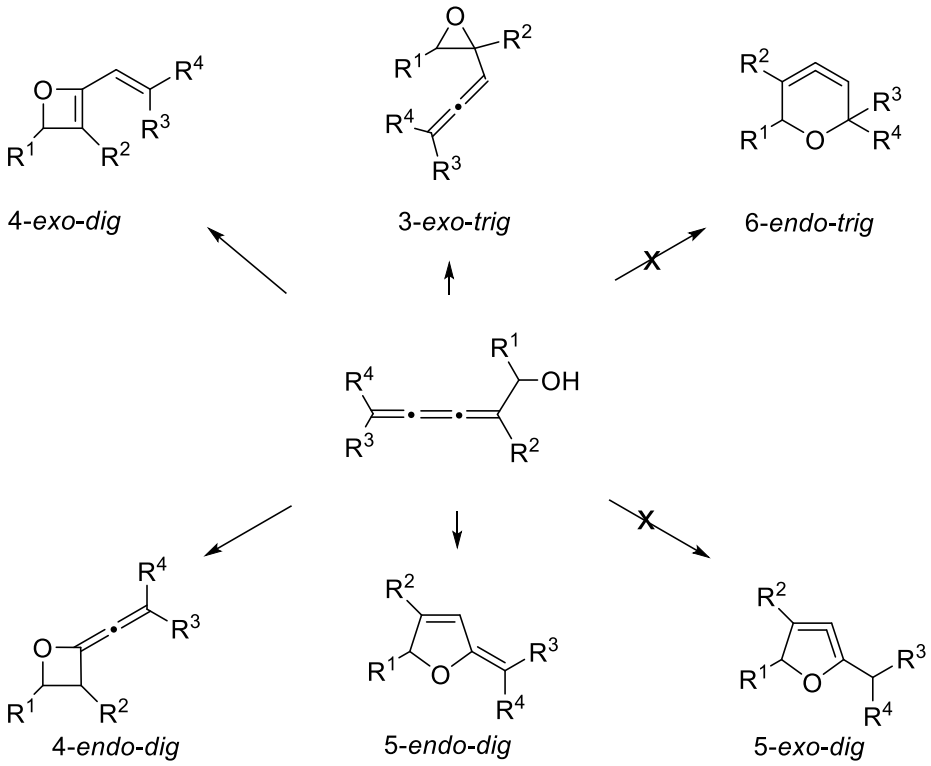
Among different strategies to build up heterocycles, cycloisomerization reactions have been studied in great detail from both synthetic and theoretical standpoints. Particularly, the catalytic intramolecular addition of a pendant nucleophile group to a cumulene functionality can be viewed as a highly efficient and atom-economical synthetic strategy. Among cumulene derivatives, 2,3-dien-1-ols are well studied,[1] while similar reactions for 2,3,4-trien-1-ols are unfamiliar.[2] Probably, this lack of reports are associated with several drawbacks such as (i) difficult-to-prepare starting materials, and (ii) how to control selectivity to get the desired adducts over undesired isomers.

Oxacyclic structures, such as furan derivatives, are found in numerous biologically active natural products.[3] Potentially, a metal-catalyzed heterocyclization reaction of α-cumulenols would produce different 3-, 4-, 5- or 6-membered oxacycles. Depending on the regioselectivity (3-*exo-trig* versus 4-*exo-dig* versus 4-*endo-dig* versus 5-*endo-dig* versus *5-exo-dig* versus *6-endo-trig* cyclization modes) any of the six possible cycloisomerization adducts could be the reaction products (Scheme X.1). However, bent cyclic allene adducts derived from *5-exo-dig* and *6-endo-trig* attacks are too constrained to be formed.[4] As a continuation of our study in this field, we decided to examine the influence of different metal activators on the cycloetherification reaction of 2,3,4-trien-1-ols, aiming for different reaction modes that can be realized in a controllable manner.

X.2.2. Results and discussion

The synthesis of oxycyclization precursors, 2,3,4-trien-1-ols **76a–e**, was accomplished via zirconium-mediated coupling reaction of 1,3-butadiynes with aldehydes using previously described methodology.[5] To explore the effects of various complexes on the metal-catalyzed heterocyclization reaction of 2,3,4-trien-1-ols, α-cumulenol **76a** was selected as model substrate. Initially, it was hoped that a catalytic activation strategy could be developed through the use of noble metal

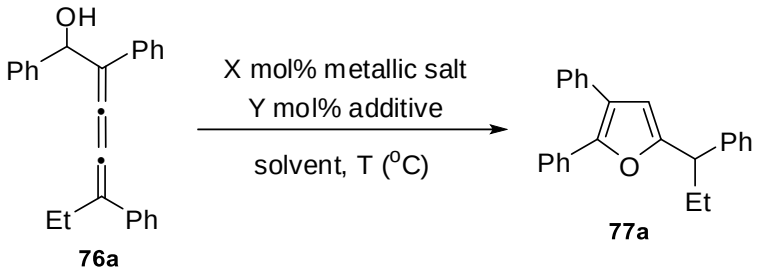
salts.[6,7] Experiments were carried out with 2,3,4-trien-1-ol **76a** using different catalysts, catalyst loading, different solvents, and temperature (Table X.1).



Scheme X.1. General scheme defining the cycloisomerizations that can take place involving α-cumulenols.

The cyclization reaction was optimized by systematically changing several reaction parameters. Lower reaction yields were observed using halogenated solvents such as dichloromethane and 1,2-dichloroethane. Among all the solvents examined, DMF and toluene proved to be the best choice. It was found that the reaction in refluxing toluene gave the best results. Unfortunately, all attempts to carry out the ring closure using platinum-based catalysis failed: decomposition products were detected in the reaction mixture after 12 h irrespective of conditions used (Table X.1, entries 1–3). Among the tested gold(I) salts, Gagosz' catalyst was the most suitable promoter (Table X.1, entry 8). Because palladium compounds are very efficient in a variety of catalytic organic transformations,[8] next, we decided to use palladium catalysis. Notably, palladium complexes proved to be a good alternative to the expensive Gagosz' catalyst. Finally, the optimal palladium-

catalyzed reaction conditions for the formation of furan **77a** turned out to be $Pd(OAc)_2$ in presence of triphenylphosphine at reflux temperature in toluene (Table X.1, entry 14).



76a **77a**

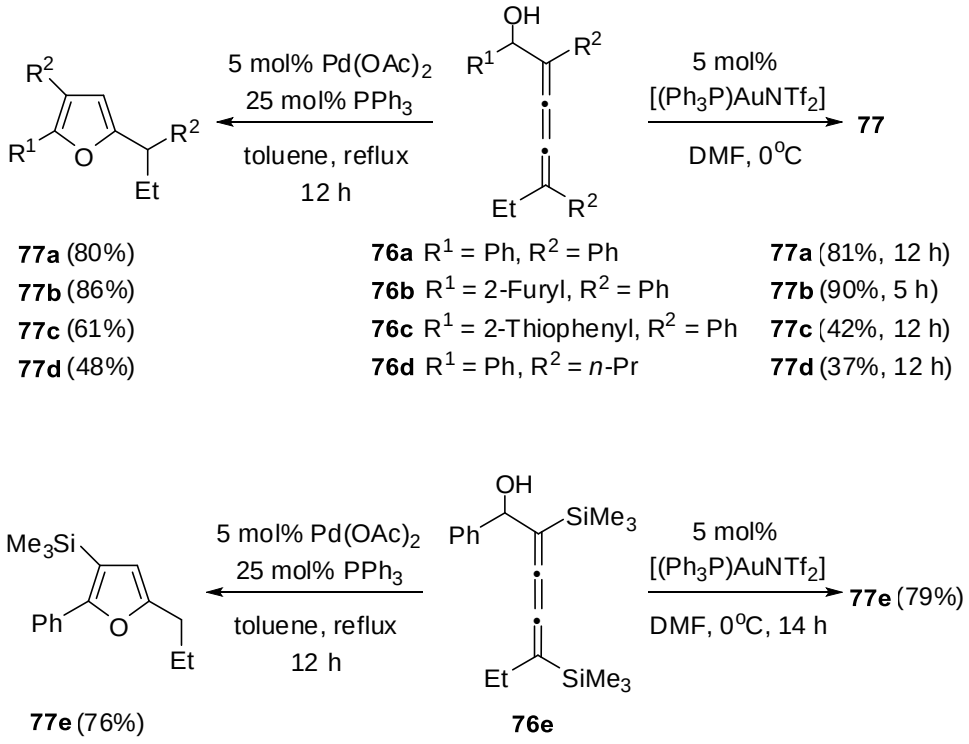
Entry	Metallic salt (mol%)	Additive (mol%)	Solvent/T (°C)	Yield[b]
1	$PtCl_2$ (1)	–	DMF/20	–
2	$PtCl_2$ (5)	AgOTf (1)	DMF/20	–
3	$PtCl_2(CH_2{=}CH_2)]_2$ (5)	TDMPP (10)	DMF/20	–
4	[IPrAuCl] (5)	$AgSbF_6$ (5)	CH_2Cl_2/20	52
5	[IPrAuCl] (5)	$AgSbF_6$ (5)	DMF/20	57
6	$[(Ph_3P)AuNTf_2]$ (5)	–	CH_2Cl_2/20	60
7	$[(Ph_3P)AuNTf_2]$ (5)	–	DMF/20	72
8	$[(Ph_3P)AuNTf_2]$ (5)	–	DMF/0	81
9	$[(Ph_3P)AuNTf_2]$ (5)	–	toluene/20	65
10	$PdCl_2$ (5)	–	toluene/20	37
11	$Pd(OAc)_2$ (5)	–	DMF/20	71
12	$Pd(OAc)_2$ (5)	–	toluene/20	43
13	$Pd(OAc)_2$ (5)	–	toluene/110	49
14	$Pd(OAc)_2$ (5)	PPh_3 (25)	toluene/110	80
15	$Pd(OAc)_2$ (3)	PPh_3 (25)	toluene/110	76
16	$Pd(OAc)_2$ (1)	PPh_3 (25)	toluene/110	48
17	$Pd(PPh_3)_4$ (5)	–	toluene/110	37

[a] DMF = *N*,*N*-dimethylformamide. TDMPP = tris(2,6-dimethoxyphenyl)phosphine. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [b] Yield of pure, isolated product with correct analytical and spectral data.

Table X.1. Selective oxycyclization reaction of 2,3,4-trien-1-ol **76a** under modified metal-catalyzed conditions.[a]

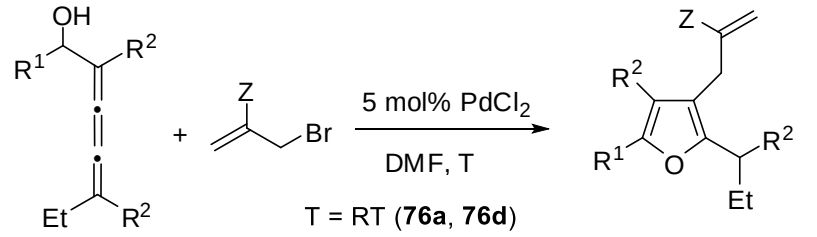
Thus, furan **77a** could be isolated after purification by column chromatography in 80% yield after $Pd(OAc)_2$ treatment. Remarkably, no water elimination was observed, indicating that this potentially serious side reaction failed to proceed at a significant rate under the above Pd-catalyzed conditions.[9] The catalyst loading was reduced to 3% without considerable erosion in the reaction yield (Table X.1, entry 15). Further reduction of the catalyst loading to 1% resulted in a reaction mixture which includes appreciable amounts of unreacted starting material (Table X.1, entry 16).

Having found the optimal reaction conditions, the scope of the oxyclization reaction was explored using differently substituted cumulative allenols. A variety of 2,3,4-trien-1-ol derivatives **76a–e** underwent a smooth Pd-catalyzed cycloisomerization to afford their corresponding trisubstituted furan products **77a–e** (Scheme X.2). These examples show that both aliphatic and aromatic substituents are well tolerated. The trimethylsilyl group linked to the aliphatic substituent in the furan adduct resulting from the cycloisomerization reaction of 2,3,4-trien-1-ol **76e** was cleavage under the mild acidic conditions of the metal-catalyzed reaction media.

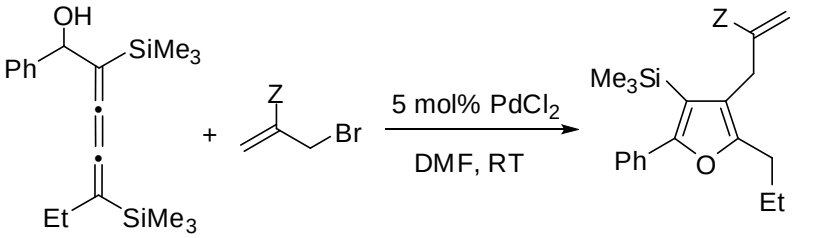


Scheme X.2. Metal-catalyzed cycloisomerization of 2,3,4-trien-1-ols **76**. Preparation of trisubstituted furans **77**.

To find whether cumulenols **76** are useful precursors not only for cycloisomerization but for cyclization/functionalization reactions, a different reactivity in the presence of a coupling partner should be attempted. The cyclization/functionalization of 2,3,4-trien-1-ols **76** was attempted using our previously optimized protocol for 2,3-dien-1-ols.[10d] In a preliminary experiment, 2,3,4-trien-1-ol **77a** was treated with allyl bromide in the presence of 5 mol% $PdCl_2$ in DMF. To our delight, the cyclization/cross-coupling reaction proceeded smoothly at room temperature to afford the corresponding tetrasubstituted furan **78aa** in 58% yield (Scheme X.3).



76a R^1 = Ph, R^2 = Ph — **78aa** Z = H (58%)
76a R^1 = Ph, R^2 = Ph — **78ab** Z = Me (57%)
76a R^1 = Ph, R^2 = Ph — **78ac** Z = Br (56%)
76b R^1 = 2-Furyl, R^2 = Ph — **78ba** Z = H (65%)
76b R^1 = 2-Furyl, R^2 = Ph — **78bb** Z = Me (79%)
76b R^1 = 2-Furyl, R^2 = Ph — **78bc** Z = Br (59%)
76c R^1 = 2-Thiophenyl, R^2 = P**65c** — **78ca** Z = H (66%)
76c R^1 = 2-Thiophenyl, R^2 = Ph — **78cb** Z = Me (67%)
76c R^1 = 2-Thiophenyl, R^2 = Ph — **78cc** Z = Br (61%)
76d R^1 = Ph, R^2 = *n*-Pr — **78da** Z = H (40%)
76d R^1 = Ph, R^2 = *n*-Pr — **78db** Z = Me (44%)
76d R^1 = Ph, R^2 = *n*-Pr — **78dc** Z = Br (30%)



76e — **78ea** Z = H (76%)
76e — **78eb** Z = Me (74%)
76e — **78ec** Z = Br (46%)

Scheme X.3. Palladium-catalyzed oxycyclization/functionalization of 2,3,4-trien-1-ols **76**. Preparation of tetrasubstituted furans **78**.

Noteworthy, oxycyclization/functionalization of the α-cumulenol subunit can be achieved when allyl bromide is added to the palladium-catalyzed transformation. Inspired by the above result, we extended this reaction sequence to various α-cumulenols **76b–e** (Scheme X.3). It was found that tetrafunctionalized furans were obtained through this heterocyclization/coupling sequence by readily adjusting the reaction temperature. Thus, the optimal reaction conditions for cumulenols **76b** and **76c** were finally established as the reaction being performed at –10 °C. The scope of this tandem Pd-catalyzed reaction was further exemplified by the coupling of both 3-bromo-2-methylprop-1-ene and 2,3-dibromoprop-1-ene with different 2,3,4-trien-1-ols (Scheme X.3). In most cases, the corresponding adducts **76aa–ec** were obtained in reasonable yields. Interestingly, the heterocyclization/cross-coupling sequence of 2,3,4-trien-1-ol **76e** bearing two sensitive TMS groups gave rise to furans **78ea–ec**, in which just the trimethylsilyl moiety directly attached to the heterocycle was retained.

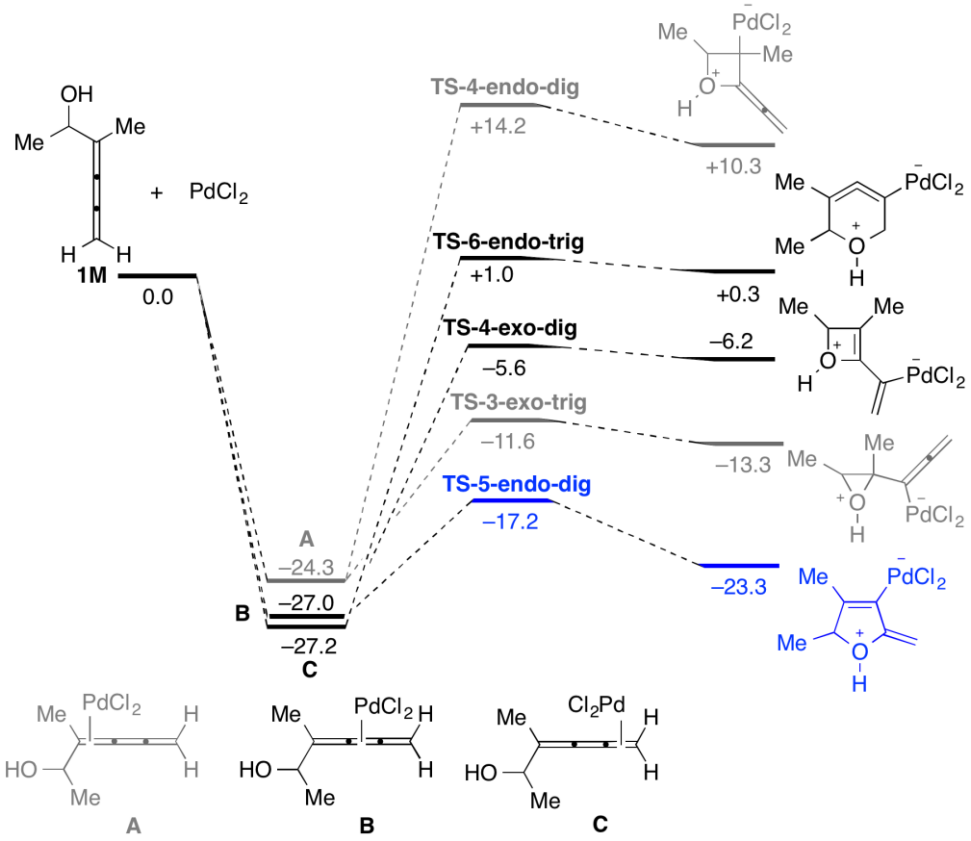


Figure X.1. Computed possible cyclization modes for the reaction between 2,3,4-trien-1-ol **1M** and $PdCl_2$. Relative free energies (ΔG, at 298 K) are given in kcal/mol. All data have been computed at the PCM(toluene)-B3LYP-D3/def2-SVP level.

Density functional theory (DFT) calculations have been carried out to gain more insight into the exclusive formation of furans **77** and the reaction mechanism involved in the subsequent coupling reaction with allyl bromides leading to furans **78**.

To this end, we first explored the different cyclization reactions from the initial intermediates **A**, **B**, **C** formed upon coordination of the $PdCl_2$ catalyst to the different C=C double bonds of the model 2,3,4-trien-1-ol **1M**. From the data gathered in Figure X.1, which shows the computed relative free energies (ΔG, at 298 K) in the presence of toluene as solvent, it becomes clear that among the different cyclization modes, the *5-endo-trig* cyclization is strongly favored under both thermodynamic and kinetic control. Moreover, the low computed activation barrier for this transformation ($\Delta G^{\neq}$ = 9.8 kcal/mol) is compatible with a process occurring at room temperature as experimentally observed (see entry 10, Table X.1)

Figure X.2 shows the reaction profiles (using DMF as solvent in the calculations) for the evolution of the zwitterionic intermediate **INT1**, the species formed through the *5-endo-trig* cyclization reaction, into the observed furans **77** and **78**, i.e. the reaction products when the process is carried out in the absence or presence of allylbromide, respectively.

Once the regioselective *5-endo-dig* cumulenic oxypalladation has occurred, intermediate **INT1** evolves to neutral dihydrofuran **INT2** by the exergonic loss of HCl (ΔG_R = –4.8 kcal/mol). Subsequent protonolysis of the C–Pd bond via transition state **TS2** leads to **INT3**, a π-complex formed by coordination of the endocyclic C=C double bond to the palladium catalyst. The ease of this reaction step is clearly reflected in the rather low activation barrier ($\Delta G^{\neq}$ = 3.2 kcal/mol) and high exergonicity (ΔG_R = –20.6 kcal/mol) computed for this transformation. Final release of the $PdCl_2$ catalyst leads to **INT4** which after isomerization produces the observed furan **2M**. The high exergonicity computed for this isomerization reaction (ΔG_R = –15.3 kcal/mol) is directly related to the aromatization of the five-membered ring, which therefore constitutes the driving force of the transformation

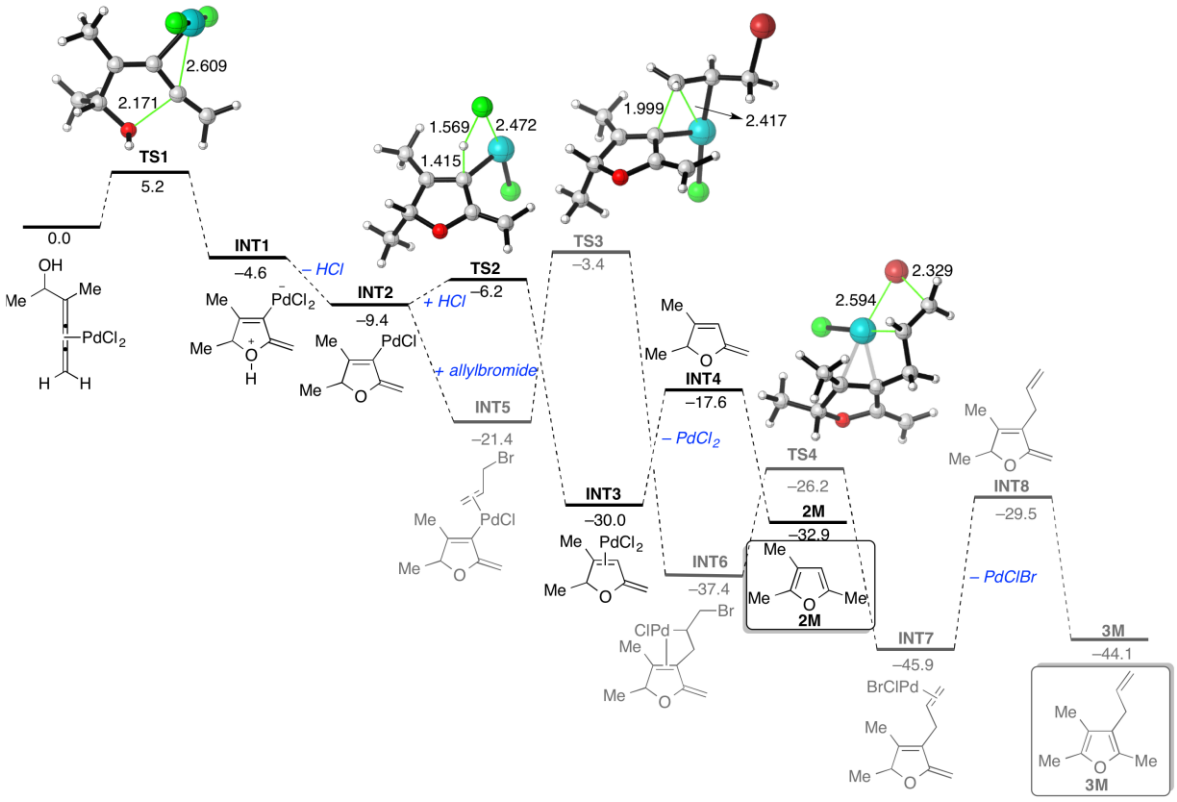
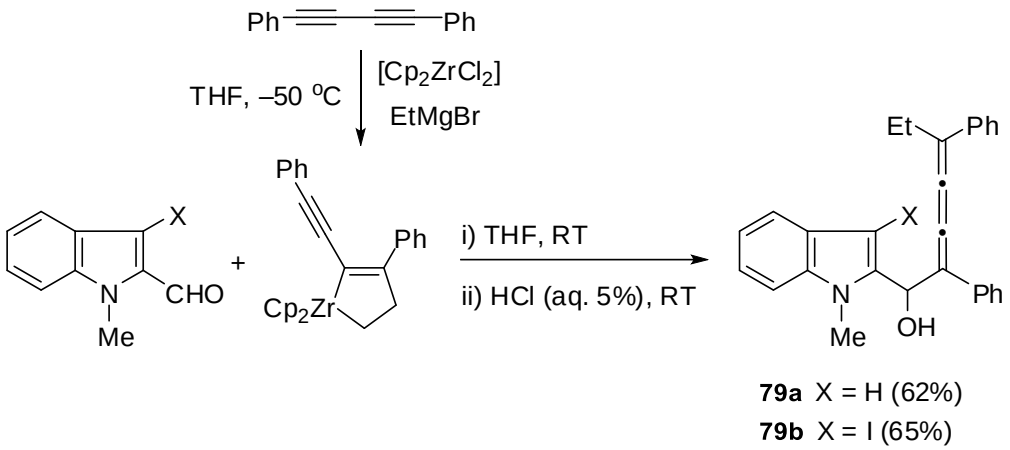


Figure X.2. Computed reaction profiles for the transformation of **INT1** into furans **2M** and **3M**. Relative free energies (ΔG, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data have been computed at the PCM(DMF)-B3LYP-D3/def2-SVP level.

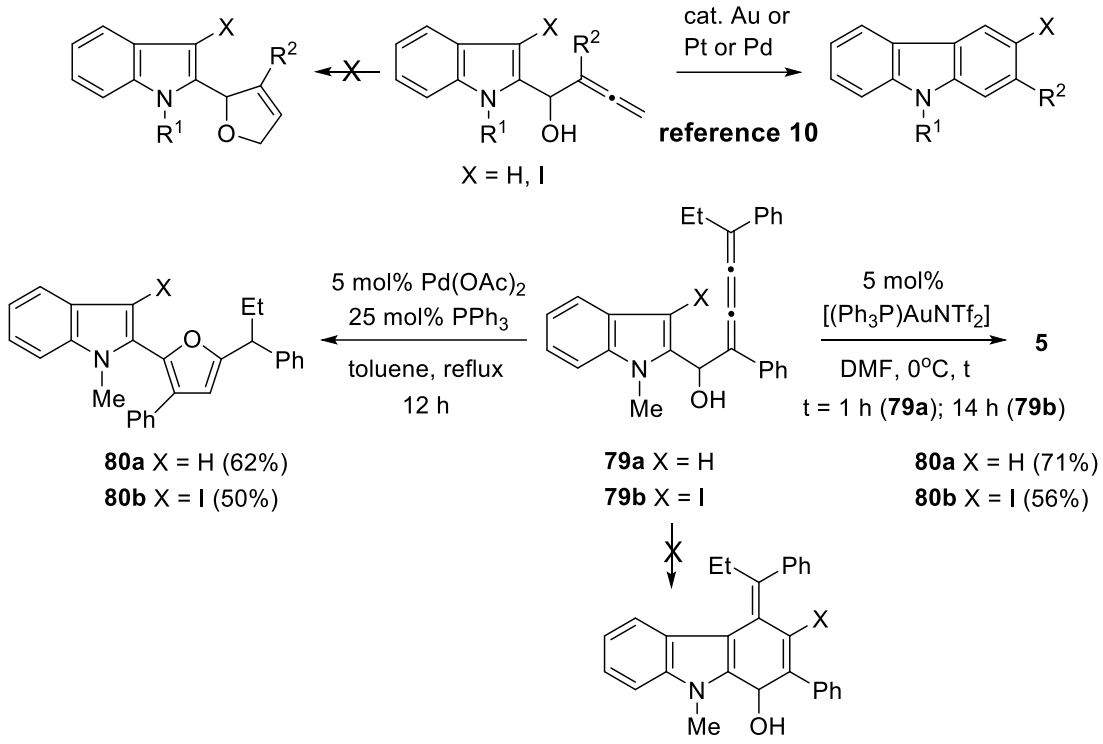
Alternatively, in the presence of allylbromide, **INT2** may evolve into **INT5** by the exergonic coordination of the allylic C=C double bond to the unsaturated transition metal fragment (ΔG_R = –12.0 kcal/mol). Subsequent insertion reaction leads to **INT6**, a new π-complex formed upon coordination of the endocyclic C=C bond to the palladium moiety. This exergonic insertion reaction (ΔG_R = –16.0 kcal/mol) proceeds through **TS3**, a saddle point associated with the formation of the new C–C bond ($\Delta G^{\neq}$ = 18.0 kcal/mol). Then, a *trans* β-bromide elimination affords the coupling adduct, 2,5-dihydrofuran **INT7**, via **TS4**, a saddle point associated with the concomitant C–Br bond rupture/Pd–Br bond formation ($\Delta G^{\neq}$ = 11.2 kcal/mol, ΔG_R = –8.5 kcal/mol). Similar to the process leading to furans **77**, final release of the PdClBr leads to **INT8** which after isomerization produces the observed furan **3M.**

As indoles are integral parts of a variety of natural products, it would be of interest to subject cumulenyl-indoles for the above metal-catalyzed conditions. We optimized the procedure for the preparation of novel indole-tethered 2,3,4-trien-1-ols **79** from 1,4-diphenylbuta-1,3-diyne and indole-2-carbaldehydes, such as 1-methyl-1*H*-indole-2-carbaldehyde and 3-iodo-1-methyl-1*H*-indole-2-carbaldehyde. Rewardingly, the zirconium-mediated coupling reactions proceeded smoothly over 12 h at RT, to afford 2,3,4-trien-1-ols **79a** and **79b** in fair yields as single regioisomers after purification in deactivated silica gel (Scheme X.4).



Scheme X.4. Zirconium-mediated synthesis of indole-tethered 2,3,4-trien-1-ols **79.**

An interesting case of selectivity arises in 2,3,4-trien-1-ols **79**, because two potentially reactive moieties, namely, alcohol and indole, are present in the same substrate. In principle, two different cyclizations (*O*- versus *C*-) can take place. Gratifyingly, it was observed that the metal-catalyzed reaction conditions using 2,3,4-trien-1-ols **76** were compatible with substrates **79**, resulting in the formation of the desired attached-ring indole-furans **80** in fair yields with complete regio- and chemoselectivity (Scheme X.5). Worthy of note, the product distribution can be completely switched in comparison with related allenyl-indoles, where the carbocyclization reaction is observed exclusively (Scheme X.5).[10]



Scheme X.5. Metal-catalyzed cycloisomerization of indole-tethered 2,3,4-trien-1-ols **79**. Preparation of indole-linked furans **80**.

The gold(I)-catalyzed preferred formation of indole-linked furans **80** over the corresponding carbocyclization products was computationally explored as well. Figure X.3 shows the computed reaction profiles for the competitive *O*- versus *C*-cyclization reactions. Our calculations suggest that the process begins with the initial coordination of the model $[AuPMe_3]^+$ catalyst to the central C=C double bond of the 2,3,4-trien-1-ol **4M** to afford the π-complex **INT8**. From this intermediate, the two possible cyclization reactions may occur. From the data in Figure X.3, it becomes clear that the observed chemoselectivity takes place under kinetic control despite the higher exergonicity computed for the C-carbocyclization reaction ($\Delta\Delta G_R$ = 17.2 kcal/mol). The computed activation barrier difference ($\Delta\Delta G^{\neq}$ = 2.4 kcal/mol) is translated into a 99/1 (O- vs C-) ratio, which nicely agrees with the experimental findings. Once the cationic complex **INT9-O** is formed, a highly exergonic (ΔG_R = –19.8 kcal/mol) deprotonation reaction mediated by the NTf_2^- base occurs to produce neutral intermediate **INT10-O**. Subsequent protonolysis of the Au–C carbon by the readily formed $NHTf_2$ produces **INT11-O** following a reaction mechanism similar to that reported by us for strongly related transformations.[11]

Once again, final decoordination of the metal fragment releases the catalyst and produces dihydrofuran **INT12-0**, which after isomerization affords the observed furan **5M**

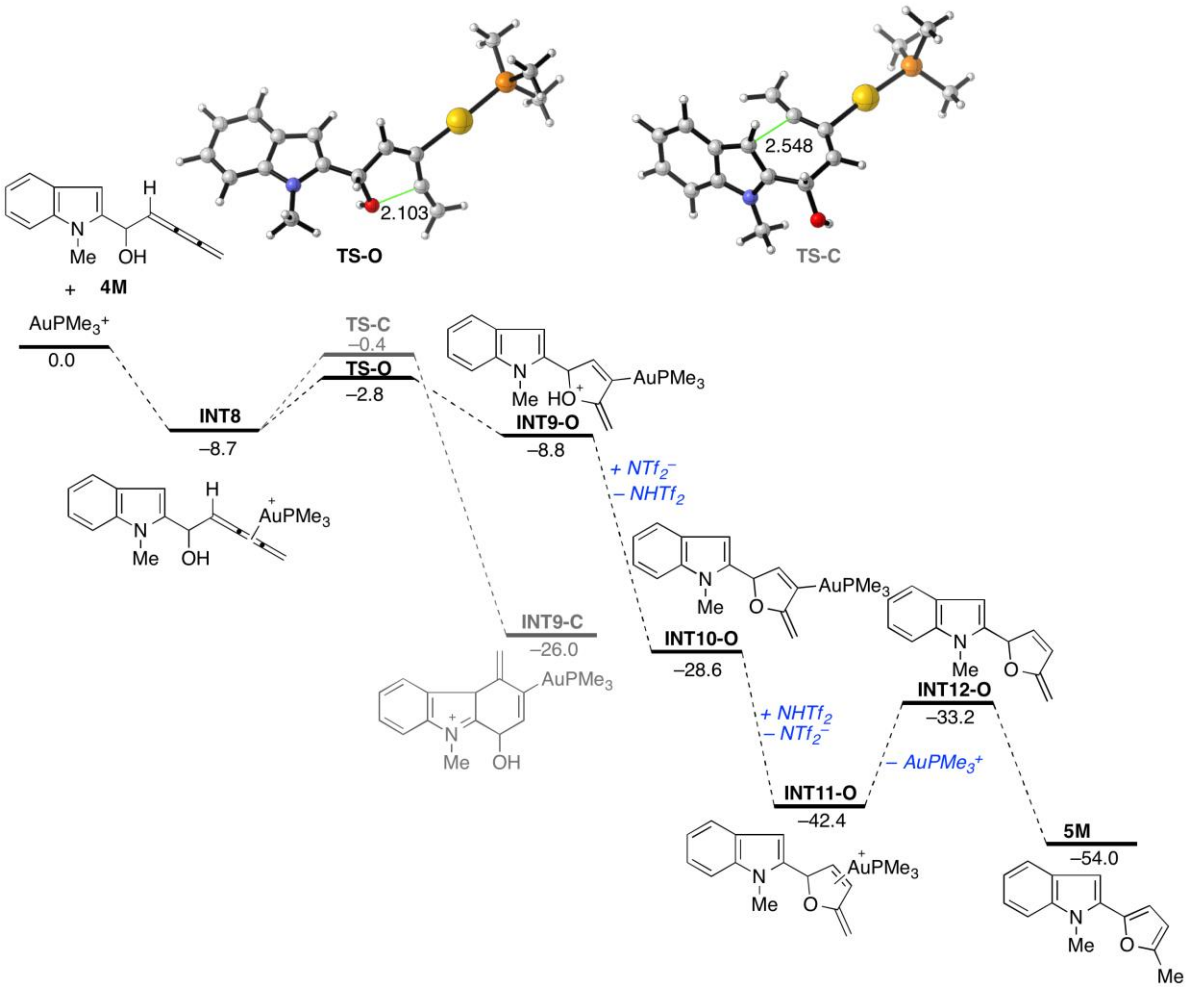
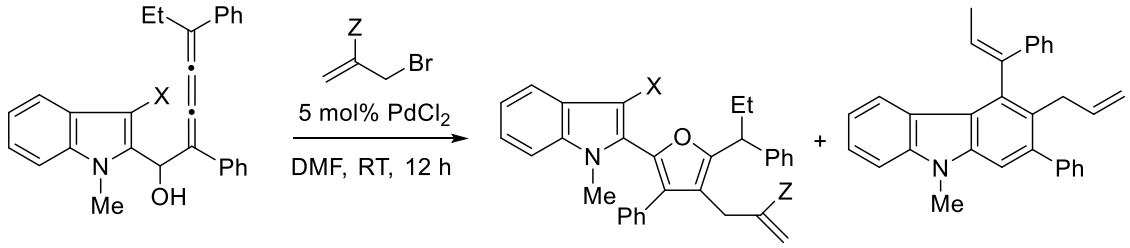


Figure X.3. Computed reaction profiles for the transformation of indol **4M** into indole-linked furan **5M**. Relative free energies (ΔG, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data have been computed at the PCM(DMF)-B3LYP-D3/def2-SVP level.

In the next experiment, the palladium-catalyzed reaction between indole-tethered 2,3,4-trien-1-ols **79** and 3-bromoprop-1-enes was studied. The reaction of indole-tethered cumulenols **79** proved to be as efficient as the reaction of more simple cumulenols **76**. The oxycyclization/functionalization sequence proceeded smoothly, selectively affording furan linked-indoles **81aa–bc** (Scheme X.6).

However, the 2,3,4-trien-1-ol **79a** when treated with allyl bromide afforded furan **81aa** as major component along with a minor product, the carbazole **82aa** (Scheme X.6). Although the chemoselectivity (oxycyclization *versus* carbocyclization) was no total in this particular case, isomers **81aa** and **82aa** were easily separated.



79a X = H
79a X = H
79a X = H
79b X = I
79b X = I
79b X = I

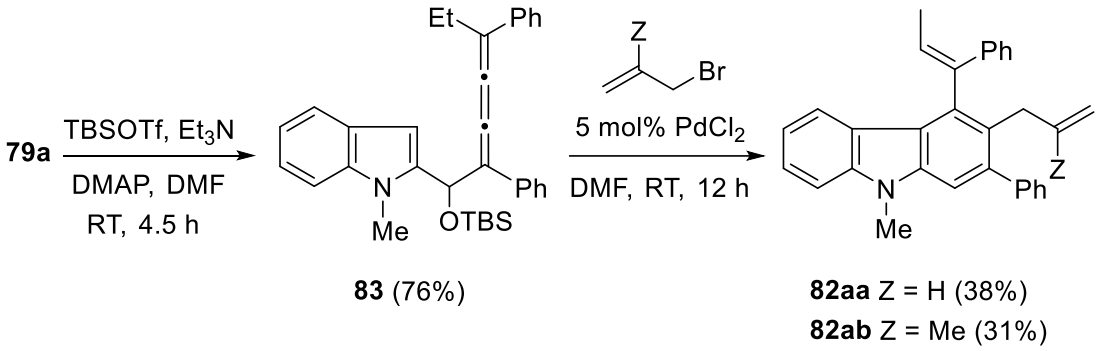
81aa Z = H (35%)
81ab Z = Me (44%)
81ac Z = Br (46%)
81ba Z = H (42%)
81bb Z = Me (61%)
81bc Z = Br (43%)

82aa (8%)

Scheme X.6. Palladium-catalyzed oxycyclization/functionalization of indole-tethered 2,3,4-trien-1-ols **79**. Preparation of tetrasubstituted indole-linked furans **81.**

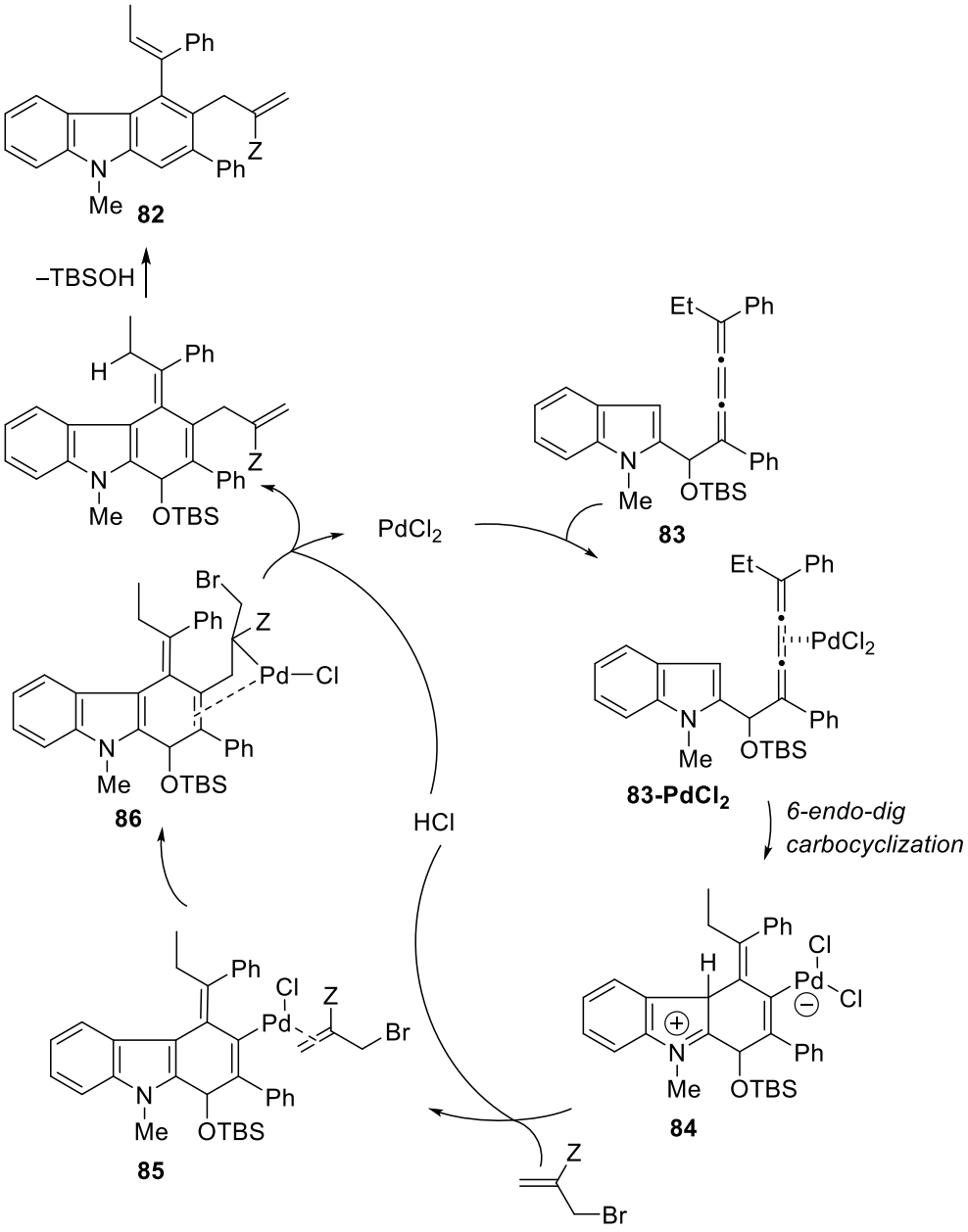
Carbazoles are an important class of heterocyclic scaffolds that exist widely in nature with interesting biological properties.[12] Moreover, the carbazole nucleus serves as a key molecular motif in materials science.[13] Development of effective methods for the construction of fuctionalized carbazoles is thus important in organic synthesis. Consequently, we decided to perform a switchable synthesis of different heterocycles, namely indole versus furan, from the same starting 2,3,4-trien-1-ol. In order to block the favored cycloetherification path, we utilized the OTBS derivative **83**, which was conveniently prepared using a standard protection protocol (Scheme X.7). Hopefully, this silyl protection should force the otherwise unfavorable hydroarylation route and make the benzannulation feasible. To check this hypothesis, (2,3,4-trien-1-yloxy)silane derivative **83** was reacted with both allyl bromide and 3-bromo-2-methylprop-1-ene under otherwise identical palladium-catalyzed conditions. To our delight, the formation of furan adducts was suppressed, according to ^{1}H NMR analysis of the crude products. As shown in Scheme X.7, the carbocyclization/coupling sequence took place to afford 2,3,4-trisubstituted carbazoles **82aa** and **82ab**. Unfortunately, some decomposition was observed on

sensitive alkenyl-carbazoles **82** during purification by flash chromatography, which may be responsible for the moderate isolated yields. Noteworthy, the use of the indole-tethered protected 2,3,4-trien-1-ol moiety changes the reactivity pattern, overcoming the oxycyclization while retaining the same regioselectivity of the cyclization step. These results could be explained through a 6-*endo-dig* hydroarylation with concomitant dehydration (see below).



Scheme X.7. Palladium-catalyzed carbocyclization/functionalization of indole-tethered (2,3,4-trien-1-yloxy)silane **83**. Preparation of trisubstituted carbazoles **82**. TBS = *tert*-butyldimethylsilyl.

According to the reaction profiles discussed above (Figures X.2 and X.3), the following mechanism for the observed Pd-catalyzed benzannulation-functionalization of indolyl (2,3,4-trien-1-yloxy)silane derivatives **83** to form carbazoles could be proposed (Scheme X.8). Initial Pd-coordination to the 2,3,4-triene moiety would produce a cumulene-palladium complex **83**-$PdCl_2$. Species **83**-$PdCl_2$ would then suffer an intramolecular chemo- and regioselective 6-*endo-dig* carbocyclization reaction to give the zwitterionic intermediate palladadihydrocarbazole **84**, which would react with the 3-bromoprop-1-ene derivative via **85** to form intermediate **86**. A *trans* β-heteroatom elimination with concurrent *tert*-butyldimethylsilanol release under the reaction conditions generates carbazoles type **82** with concomitant regeneration of the palladium catalyst (Scheme X.8).



Scheme X.8. Mechanistic explanation for the palladium-catalyzed carbocyclization/functionalization of indole-tethered 2,3,4-triene **83**.

X.2.3. Conclusion

In conclusion, the controlled preparation of tri- and tetrasubstituted furans, as well as carbazoles has been achieved through chemo- and regioselective metal-catalyzed cyclization reactions of cumulenic alcohols. Chemo- and regiocontrol issues are influenced neither by the nature of the tether or the metal catalyst. Computational investigations allow the rationalization of this reactivity.

X.3. Experimental Section

General methods: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, Bruker Avance-300 or Varian VRX-300S. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{1}H, 7.27 ppm; ^{13}C, 76.9 ppm), or acetone-d_6 (^{1}H, 2.0 ppm; ^{13}C, 206.3 ppm), or C_6D_6 (^{1}H, 7.16 ppm; ^{13}C, 128.0 ppm). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. All commercially available compounds were used without further purification.

General procedure for the Pd^{II}-catalyzed cycloisomerization of 2,3,4-trien-1-ols 76 and 79. Preparation of trisubstituted furans 77 and 80. Method A. $Pd(OAc)_2$ (0.05 mmol) and (Ph_3P) (0.25 mmol) were sequentially added to a stirred solution of the appropriate 2,3,4-trien-1-ol **76** or **79** (1.0 mmol) in toluene (10 mL) under argon. The resulting mixture was stirred at reflux temperature until disappearance of the starting material (TLC, typically 12 hours). The reaction mixture was allowed to cool to room temperature and it was filtered through a celite pad. The reaction was then quenched with brine (1.0 mL) and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed twice with brine and dried ($MgSO_4$). The solution was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave adducts **77** or **80**. Spectroscopic and analytical data for pure forms of **77** or **80** follow.[14]

General procedure for the Au^{I}-catalyzed cycloisomerization of 2,3,4-trien-1-ols 76 and 79. Preparation of trisubstituted furans 77 and 80. Method B. [(Ph_3P)$AuNTf_2$] (0.05 mmol) was added to a stirred solution of the appropriate 2,3,4-trien-1-ol **76** or **79** (1.0 mmol) in *N*,*N*-dimethylformamide (10 mL) at 0^{o}C under argon. The resulting mixture was stirred at 0^{o}C until disappearance of the starting material (TLC, 1–14 hours). The reaction mixture was filtered through a celite pad. Water (5 mL) was added to the filtrate before being extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed twice with brine and dried ($MgSO_4$). The solution was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave adducts **77** or **80**. Spectroscopic and analytical data for pure forms of **77** or **80** follow.

3-Phenyl-5-(1-phenylpropyl)-2,2'-bifuran 77b. From 86 mg (0.30 mmol) of 2,3,4-trien-1-ol **76b**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **77b** (85 mg, 86%, method A; 89 mg, 90%, method B) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.40 (dd, 2H, *J* = 8.5, 1.5 Hz, Ar), 7.26 (m, 9H, Ar), 6.37 (dd, 1H, *J* = 3.5, 0.7 Hz, Ar), 6.31 (dd, 1H, *J* = 3.4, 1.8 Hz, Ar), 6.13 (d, 1H, *J* = 0.7 Hz, Ar), 3.81 (t, 1H, *J* = 7.6 Hz, CH), 2.15 (m, 1H, *J* = 7.2 Hz, C*H*H), 1.89 (m, 1H, *J* = 7.2 Hz, CH*H*), 0.88 (t, 3H, *J* = 7.3 Hz, Me); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ^{o}C) δ: 157.8, 146.4, 142.2, 141.6 (Ar, CH), 139.6, 133.5, 128.5 (Ar, 4CH), 128.3 (Ar, 2CH), 128.0 (Ar, 2CH), 127.1 (Ar, CH), 126.6 (Ar, CH), 123.2, 111.1 (Ar, CH), 109.1 (Ar, CH), 106.8 (Ar, CH), 47.2 (CH), 28.0 (CH_2), 12.4 (Me); IR ($CHCl_3$, cm^{-1}): ν 2930, 1690, 1432, 1356, 740, 696; HRMS (ES): calcd for $C_{23}H_{20}O_2$ [*M*]$^{+}$: 328.1463; found: 328.1458.

3-Phenyl-5-(1-phenylpropyl)-2-(thiophen-2-yl)furan 77c. From 48 mg (0.14 mmol) of 2,3,4-trien-1-ol **76c**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **77c** (29 mg, 61%, method A; 20 mg, 42%, method B) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ: 7.39 (dd, 2H, *J* = 8.3, 1.6 Hz, Ar), 7.28 (m, 7H, Ar), 7.20 (m, 1H, Ar), 7.09 (dd, 1H, *J* = 5.1, 1.0 Hz, Ar), 7.06 (dd, 1H, *J* = 3.7,

1.0 Hz, Ar), 6.87 (dd, 1H, *J* = 5.0, 3.7 Hz, Ar), 6.09 (s, 1H, Ar), 3.81 (t, 1H, *J* = 7.6 Hz, CH), 2.15 (m, 1H, *J* = 7.3 Hz, C*H*H), 1.92 (m, 1H, *J* = 7.4 Hz, CH*H*), 0.90 (t, 3H, *J* = 7.3 Hz, Me); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 157.2, 142.9, 142.2, 133.9, 133.5, 128.7 (Ar, 4CH), 128.5 (Ar, 2CH), 128.0 (Ar, 2CH), 127.3 (Ar, CH), 127.1 (Ar, CH), 126.6 (Ar, CH), 124.2 (Ar, CH), 123.6 (Ar, CH), 122.6, 109.7 (Ar, CH), 47.2 (CH), 28.0 (CH_2), 12.4 (Me); IR ($CHCl_3$, cm^{-1}): ν 2945, 1587, 1349, 753, 699; HRMS (ES): calcd for $C_{23}H_{20}OS$ [*M*]$^+$: 344.1235; found: 344.1236.

1-Methyl-2-[3-phenyl-5-(1-phenylpropyl)furan-2-yl]-1*H*-indole 80a. From 31 mg (0.08 mmol) of 2,3,4-trien-1-ol **79a**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **80a** (19 mg, 62%, method A; 22 mg, 71%, method B) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.52 (d, 1H, *J* = 7.7 Hz, Ar), 7.28 (m, 6H, Ar), 7.18 (m, 6H, Ar), 7.05 (t, 1H, *J* = 7.3 Hz, Ar), 6.56 (s, 1H, Ar), 6.34 (s, 1H, Ar), 3.85 (t, 1H, *J* = 7.7 Hz, CH), 3.44 (s, 3H, NMe), 2.17 (m, 1H, *J* = 7.3 Hz, C*H*H), 1.95 (m, 1H, *J* = 7.6 Hz, CH*H*), 0.92 (t, 3H, *J* = 7.3 Hz, Me); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 158.7, 147.2, 140.2, 137.8, 133.4, 130.9, 128.5 (Ar, 2CH), 128.4 (Ar, 2CH), 128.0, 127.7 (Ar, 2CH), 127.5 (Ar, 2CH), 126.9 (Ar, CH), 126.7 (Ar, CH), 125.7, 122.1 (Ar, CH), 120.9 (Ar, CH), 119.7 (Ar, CH), 109.5 (Ar, CH), 107.8 (Ar, CH), 103.5 (Ar, CH), 47.4 (CH), 31.0 (NMe), 27.7 (CH_2), 12.4 (Me); IR ($CHCl_3$, cm^{-1}): ν 2924, 1764, 1676, 1457, 753, 700; HRMS (ES): calcd for $C_{28}H_{25}NO$ [*M*]$^+$: 391.1936; found: 391.1935.

General procedure for the Pd^{II}-catalyzed heterocyclization/cross-coupling of 2,3,4-trien-1-ols 76 and 79 with bromoprop-1-enes. Preparation of tetrasubstituted furans 78 and 81. Palladium(II) chloride (0.05 mmol) was added to a stirred solution of the appropriate 2,3,4-trien-1-ol **76** or **79** (1.0 mmol) and the corresponding bromoprop-1-ene derivative (3.0 mmol) in *N*,*N*-dimethylformamide (6.0 mL). The reaction was stirred under argon atmosphere at the appropriate temperature (RT or –10ºC) until disappearance of the starting material (TLC, typically 12 hours). Water (3.0 mL) was added before being extracted with ethyl acetate (3 x 10 mL). The organic phase was washed with water (2 x 4 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure adducts **78** and **81**.

3-(2-Methylallyl)-4,5-diphenyl-2-(1-phenylpropyl)furan 78ab. From 53 mg (0.16 mmol) of 2,3,4-trien-1-ol **76a**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **78ab** (35 mg, 57%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.32 (m, 4H, Ar), 7.24 (m, 4H, Ar), 7.13 (m, 7H, Ar), 4.60 (dd, 1H, *J* = 1.9, 1.3 Hz, =C*H*H), 4.43 (d, 1H, *J* = 1.0 Hz, =CH*H*), 3.80 (t, 1H, *J* = 7.7 Hz, CH), 2.83 (s, 2H, CH_2), 2.17 (m, 1H, *J* = 7.9 Hz, C*H*H), 2.01 (m, 1H, *J* = 7.3 Hz, CH*H*), 1.59 (s, 3H, Me), 0.86 (t, 3H, *J* = 7.3 Hz, Me); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 152.3, 146.4, 144.0, 143.1, 134.2 131.5, 130.1 (Ar, 2CH), 128.5 (Ar, 2CH), 128.3 (Ar, 2CH), 128.2 (Ar, 2CH), 128.0 (Ar, 2CH), 127.1 (Ar, CH), 126.5 (Ar, CH), 126.3 (Ar, CH), 125.0 (Ar, 2CH), 124.2, 119.3, 111.3 (=CH_2), 45.3 (CH), 31.3 (CH_2), 28.4 (CH_2), 22.6 (Me), 12.8 (Me); IR ($CHCl_3$, cm^{-1}): ν 2943, 1789, 1654, 1432, 757, 710; HRMS (ES): calcd for $C_{29}H_{28}O$ [*M*]$^+$: 392.2140; found: 392.2133.

4-Allyl-3-phenyl-5-(1-phenylpropyl)-2,2'-bifuran 78ba. From 50 mg (0.15 mmol) of 2,3,4-trien-1-ol **76b**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **78ba** (36 mg, 65%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ºC) δ: 7.43 (d, 2H, *J* = 7.2 Hz, Ar), 7.28 (d, 2H, *J* = 8.2 Hz, Ar), 7.11 (m, 6H, Ar), 6.95 (d, 1H, *J* = 1.8 Hz, Ar), 6.28 (d, 1H, *J* = 3.4 Hz, Ar), 5.98 (dd, 1H, *J* = 1.8, 3.4 Hz, Ar), 5.66 (m, 1H, =CH), 4.85 (m, 2H, =CH_2), 3.86 (t, 1H, *J* = 7.2 Hz, CH), 2.99 (dd, 2H, *J* = 5.7, 1.3 Hz, CH_2), 2.34 (m, 1H, *J* = 7.3 Hz, C*H*H), 2.07 (m, 1H, *J* = 7.2 Hz, CH*H*), 0.91 (t,

3H, *J* = 7.3 Hz, Me); ^{13}C-NMR (75 MHz, C_6D_6, 25 ºC) δ: 153.0, 141.2, 143.4, 141.7 (Ar, CH), 136.8 (=CH), 133.5, 130.5, (Ar, 2CH), 128.9 (Ar, 2CH), 127.6 (Ar, 4CH), 126.8 (Ar, 2CH), 119.2, 115.4 (=CH_2), 111.3 (Ar, CH), 106.3 (Ar, CH), 45.9(CH), 28.5 (CH_2), 27.7 (CH_2), 12.9 (Me); IR ($CHCl_3$, cm^{-1}): ν 2926, 1767, 1670, 1452, 760, 701; HRMS (ES): calcd for $C_{26}H_{24}O_2$ [*M*]$^+$: 368.1776; found: 368.1788.

4-(2-Bromoallyl)-3-phenyl-5-(1-phenylpropyl)-2,2'-bifuran 78bc. From 29 mg (0.09 mmol) of 2,3,4-trien-1-ol **76b**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **78bc** (24 mg, 59%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 7.32 (m, 11H, Ar), 6.34 (dd, 1H, *J* = 3.4, 1.7 Hz, Ar), 6.24 (dd, 1H, *J* = 3.4, 0.7 Hz, Ar), 5.35 (d, 1H, *J* = 1.7 Hz, =C*H*H), 5.30 (d, 1H, *J* = 1.7 Hz, =CH*H*), 3.88 (t, 1H, *J* = 7.7 Hz, CH), 3.40 (s, 2H, CH_2), 2.24 (m, 1H, *J* = 7.3 Hz, C*H*H), 2.09 (m, 1H, *J* = 7.3 Hz, CH*H*), 0.95 (t, 3H, *J* = 7.3 Hz, Me); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ: 153.5, 146.4, 144.4, 143.6, 141.5 (Ar, CH), 140.4, 131.5, 129.8 (Ar, 2CH), 128.4 (Ar, 2CH), 128.3 (Ar, 2CH), 128.0 (Ar, 2CH), 127.5 (Ar, CH), 126.5 (Ar, CH), 126.4, 117.5 (=CH_2), 117.2, 111.0 (Ar, CH), 106.0 (Ar, CH), 45.5 (CH), 35.6 (CH_2), 28.1 (CH_2), 12.7 (Me); IR ($CHCl_3$, cm^{-1}): ν 2945, 1754, 1643, 1432, 756, 697; HRMS (ES): calcd for $C_{26}H_{23}O_2Br$ [*M*]$^+$: 446.0881; found: 446.0880.

3-(2-Bromoallyl)-4-phenyl-2-(1-phenylpropyl)-5-(thiophen-2-yl)furan 78cc. From 50 mg (0.14 mmol) of 2,3,4-trien-1-ol **76c**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **78cc** (38 mg, 61%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ºC) δ: 7.37 (d, 2H, *J* = 7.2 Hz, Ar), 7.11 (m, 9H, Ar), 6.66 (dd, 1H, *J* = 5.0, 1.0 Hz, Ar), 6.58 (d, 1H, *J* = 5.1, 3.7 Hz, Ar), 5.18 (d, 1H, *J* = 1.5 Hz, =C*H*H), 5.07 (d, 1H, *J* = 1.7 Hz, =CH*H*), 3.79 (t, 1H, *J* = 7.7 Hz, CH), 3.30 (m, 2H, CH_2), 2.28 (m, 1H, *J* = 7.6 Hz, C*H*H), 2.04 (m, 1H, *J* = 7.3 Hz, CH*H*), 0.88 (t, 3H, *J* = 7.3 Hz, Me); ^{13}C-NMR (75 MHz, C_6D_6, 25 ºC) δ: 153.4, 144.3, 142.8, 134.0, 133.0, 131.9, 130.5 (Ar, 2CH), 128.9 (Ar, 4CH), 127.4 (Ar, 2CH), 126.9 (Ar, CH), 125.2 (Ar, 2CH), 124.1 (Ar, CH), 123.3 (Ar, CH), 118.2, 117.8 (=CH_2), 45.9 (CH), 36.0 (CH_2), 28.6 (CH_2), 12.9 (Me); IR ($CHCl_3$, cm^{-1}): ν 2920, 1754, 1672, 1434, 780, 700; HRMS (ES): calcd for $C_{26}H_{23}OSBr$ [*M*]$^+$: 462.0653; found: 462.0669.

Trimethyl[4-(2-methylallyl)-2-phenyl-5-propylfuran-3-yl]silane 78eb. From 49 mg (0.15 mmol) of 2,3,4-trien-1-ol **76e**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **78eb** (35 mg, 74%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ºC) δ: 7.75 (dd, 2H, *J* = 8.5, 1.5 Hz, Ar), 7.10 (m, 3H, Ar), 5.88 (m, 1H, =CH), 4.86 (m, 2H, =CH_2), 3.11 (s, 2H, CH_2), 2.50 (m, 2H, CH_2), 1.65 (s, 3H, Me), 1.62 (m, 2H, CH_2), 0.87 (t, 3H, *J* = 7.3 Hz, Me), 0.27 (s, 9H, $SiMe_3$); ^{13}C-NMR (75 MHz, C_6D_6, 25 ºC) δ: 153.0, 145.0, 134.3, 128.9 (Ar, 2CH), 126.9 (Ar, CH), 123.7 (Ar, 2CH), 122.2, 119.3, 111.7 (=CH_2), 108.1, 30.2 (CH_2), 28.2 (CH_2), 23.3 (CH_2), 23.2 (Me), 14.1 (Me), 1.1 ($SiMe_3$); IR ($CHCl_3$, cm^{-1}): ν 2930, 1734, 1654, 1421, 745, 695; HRMS (ES): calcd for $C_{20}H_{28}OSi$ [*M*]$^+$: 312.1909; found: 312.1906.

2-[4-(2-Bromoallyl)-3-phenyl-5-(1-phenylpropyl)furan-2-yl]-1-methyl-1*H*-indole 81ac. From 75 mg (0.19 mmol) of indole-tethered 2,3,4-trien-1-ol **79a**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **81ac** (45 mg, 46%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ºC) δ: 7.59 (d, 1H, *J* = 7.9 Hz, Ar), 7.45 (d, 2H, *J* = 7.2 Hz, Ar), 7.32 (m, 3H, Ar), 7.16 (m, 8H, Ar), 6.75 (d, 1H, *J* = 0.7 Hz, Ar), 5.39 (d, 1H, *J* = 1.6 Hz, =C*H*H), 5.33 (d, 1H, *J* = 1.7 Hz, =CH*H*), 3.96 (t, 1H, *J* = 7.9 Hz, CH), 3.35 (s, 3H, NMe), 3.32 (m, 2H, CH_2), 2.36 (m, 1H, *J* = 7.2 Hz, C*H*H), 2.15 (m, 1H, *J* = 7.0 Hz, CH*H*), 1.00 (t, 3H, *J* = 7.3 Hz, Me); ^{13}C-NMR (75 MHz, C_6D_6, 25 ºC) δ: 154.8, 142.7, 142.2, 138.4, 133.3, 132.1, 130.6, 129.8 (Ar, 2CH), 129.3 (Ar, 2CH), 128.7 (Ar, 2CH), 128.6 (Ar, 2CH), 128.1 (Ar, CH), 127.0 (Ar, CH), 126.5 (2C), 122.5 (Ar,

CH), 121.3 (Ar, CH), 120.4 (Ar, CH), 117.9 (=CH_2), 117.3, 109.8 (Ar, CH), 103.9 (Ar, CH), 45.8 (CH), 34.9 (CH_2), 31.2 (NMe), 28.0 (CH_2), 12.8 (Me); IR ($CHCl_3$, cm^{-1}): ν 2932 , 1709, 1623, 1356, 746, 699; HRMS (ES): calcd for $C_{31}H_{28}BrNO$ [*M*]$^+$: 509.1354; found: 509.1351.

2-[4-Allyl-3-phenyl-5-(1-phenylpropyl)furan-2-yl]-3-iodo-1-methyl-1*H*-indole 81ba. From 47 mg (0.09 mmol) of indole-tethered 2,3,4-trien-1-ol **79b**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **81ba** (21 mg, 42%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.76 (m, 1H, Ar), 7.46 (d, 2H, *J* = 7.4 Hz, Ar), 7.16 (m, 7H, Ar), 6.94 (m, 3H, Ar),6.79 (m, 1H, Ar), 5.83 (m, 1H, =CH), 4.98 (m, 2H, =CH_2), 3.91 (t, 1H, *J* = 7.0 Hz, CH), 3.17 (d, 2H, *J* = 5.4 Hz, CH_2), 2.79 (d, 3H, *J* = 6.5 Hz, NMe), 2.36 (m, 1H, *J* = 7.3 Hz, C*H*H), 2.08 (m, 1H, *J* = 7.1 Hz, CH*H*), 0.96 (q, 3H, *J* = 7.5 Hz, Me); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 155.7, 143.3, 138.5, 137.2, 137.1 (=CH), 133.3, 131.1, 130.1, 129.7 (Ar, 2CH), 129.3 (Ar, 2CH), 129.2 (Ar, 2CH), 128.7 (Ar, 2CH), 127.8 (Ar, CH), 126.9 (Ar,CH), 123.6 (Ar, CH), 121.1, 121.0 (Ar, CH), 120.0 (Ar, CH), 117.8, 116.7, 115.8 (=CH_2), 110.2 (Ar, CH), 46.0 (CH), 30.8 (NMe), 28.7 (CH_2), 28.0 (CH_2), 13.0 (Me); IR ($CHCl_3$, cm^{-1}): ν 2925 , 1712, 1611, 1364, 752, 702; HRMS (ES): calcd for $C_{31}H_{28}NOI$ [*M*]$^+$: 557.1216; found: 557.1197.

3-Iodo-1-methyl-2-[4-(2-methylallyl)-3-phenyl-5-(1-phenylpropyl)furan-2-yl]-1*H*-indole 81bb. From 80 mg (0.16 mmol) of indole-tethered 2,3,4-trien-1-ol **79b**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **81bb** (56 mg, 61%) as a colorless oil; ^{1}H-NMR (300 MHz, C_6D_6, 25 ^{o}C) δ: 7.80 (m, 1H, Ar), 7.61 (d, 2H, *J* = 7.1 Hz, Ar), 7.30 (m, 7H, Ar), 7.06 (m, 3H, Ar), 6.92 (m, 1H, Ar), 5.00 (s, 1H, =C*H*H), 4.95 (s, 1H, =CH*H*), 4.06 (t, 1H, *J* = 7.3 Hz, CH), 3.18 (s, 2H, CH_2), 2.95 (s, 3H, NMe), 2.50 (m, 1H, *J* = 7.2 Hz, C*H*H), 2.23 (m, 1H, *J* = 7.0 Hz, CH*H*), 1.74 (s, 3H, Me), 1.10 (t, 3H, *J* = 7.4 Hz, Me); ^{13}C-NMR (75 MHz, C_6D_6, 25 ^{o}C) δ: 154.1, 147.9, 146.1, 144.2, 138.5, 134.0, 131.0, 129.8 (Ar, 2CH), 129.4, 129.2 (Ar, 2CH), 129.1 (Ar, 2CH), 129.0 (Ar, CH), 127.5 (Ar, CH), 127.1 (Ar, CH), 122.4 121.3 (Ar, CH), 120.3 (Ar, CH), 118.7 (Ar, CH), 111.9 (=CH_2), 109.8 (Ar, CH), 103.8 (Ar, CH), 45.8 (CH), 31.9 (CH_2), 31.1 (NMe), 28.6 (CH_2), 13.0 (Me); IR ($CHCl_3$, cm^{-1}): ν 2918 , 1728, 1623, 1369, 749, 697; HRMS (ES): calcd for $C_{32}H_{30}NOI$ [*M*]$^+$: 571.1372; found: 571.1349.

General procedure for the Pd^{II}-catalyzed carbocyclization/cross-coupling of protected 2,3,4-trien-1-ol 83 with bromoprop-1-enes. Preparation of trisubstituted carbazoles 82. Palladium(II) chloride (0.005 mmol) was added to a stirred solution of the protected 2,3,4-trien-1-ol **83** (0.10 mmol) and the corresponding bromoprop-1-ene derivative (0.30 mmol) in *N*,*N*-dimethylformamide (0.6 mL). The reaction was stirred under argon atmosphere at room temperature until disappearance of the starting material (TLC, 12 h). Water (0.5 mL) was added before being extracted with ethyl acetate (3 x 3 mL). The organic phase was washed with water (2 x 1 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure adducts **82**.

(*E*)-9-Methyl-3-(2-methylallyl)-2-phenyl-4-(1-phenylprop-1-enyl)-9*H*-carbazole 82ab. From 54 mg (0.11 mmol) of protected 2,3,4-trien-1-ol **83**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **82ab** (15 mg, 31%) as a colorless oil; ^{1}H-NMR (300 MHz, acetone-d_6, 25 ^{o}C) δ: 8.05 (d, 1H, *J* = 7.9 Hz, Ar), 7.55 (d, 1H, *J* = 8.2 Hz, Ar), 7.38 (m, 9H, Ar), 7.24 (t, 1H, *J* = 7.4 Hz, Ar), 7.19 (t, 1H, *J* = 7.4 Hz, Ar), 7.03 (t, 1H, *J* = 7.6 Hz, Ar), 6.60 (q, 1H, *J* = 6.8 Hz, =CH), 4.48 (s, 1H, =C*H*H), 4.13 (s, 1H, =CH*H*), 3.97 (s, 3H, NMe), 3.20 (q, 2H, *J* = 12.9 Hz, CH_2), 1.52 (d, 3H, *J* = 7.0 Hz, Me), 1.38 (s, 3H, Me); ^{13}C-NMR (75 MHz, acetone-d_6, 25 ^{o}C) δ: 146.0, 144.3, 142.7, 142.1, 140.6, 140.5, 135.0, 130.3 (Ar, 2CH), 129.2 (Ar, 2CH), 128.6 (Ar, 2CH), 127.6 (Ar, CH), 127.5 (Ar, CH), 127.3, 126.8 (Ar, 2CH), 126.4 (Ar, CH), 126.4 (=CH), 123.4, 122.4 (Ar,

CH), 121.3, 119.7 (Ar, CH), 111.5 (=CH_2), 110.4 (Ar, CH), 109.4 (Ar, CH), 38.2 (CH_2), 30.1 (NMe), 16.1 (Me); IR ($CHCl_3$, cm^{-1}): ν 2930, 1464, 1313, 1180, 787, 661; HRMS (ES): calcd for $C_{32}H_{29}N$ [*M*]$^+$: 427.2300; found: 427.2313.

Computational Details: All the calculations reported in this paper were performed with the Gaussian 09 suite of programs.[15] Electron correlation was partially taken into account using the hybrid functional usually denoted as B3LYP[16] in conjunction with the D3 dispersion correction suggested by Grimme et al.[17] using the double-ζ quality plus polarization def2-SVP[18] basis set for all atoms. Reactants and products were characterized by frequency calculations,[19] and have positive definite Hessian matrices. Transition structures (TS's) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the Intrinsic Reaction Coordinate (IRC) method.[20] Solvents effects were taken into account using the Polarizable Continuum Model (PCM)[21] during the geometry optimizations. This level is denoted PCM-(solvent)-B3LYP-D3/def2-SVP.

X.4. Notes and references

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XI. DISCUSIÓN GENERAL

XI. DISCUSIÓN GENERAL

XI.1. Reacciones de carbociclación de alenos catalizadas por metales de transición.

A lo largo de este trabajo se han desarrollado diferentes metodologías de carbociclación catalizadas por oro y paladio de alenos unidos a núcleos de importancia biológica como las β-lactamas, los azúcares y el indol.

XI.1.1. Capítulo 1: Estudio de la reactividad catalizada por oro de ariloxialenos: 9-*endo* carbociclación frente a 5-*exo* hidroalquilación

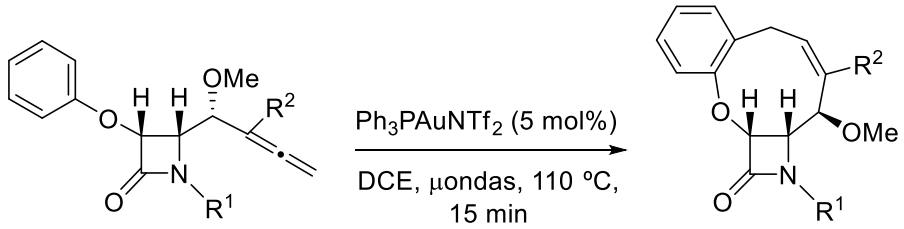
En este Capítulo se ha abordado el estudio de la reacción de carbociclación catalizada por oro, en α-alenoles *O*-protegidos unidos tanto al núcleo de 2-azetidinona como de glucofuranosa.

En primer lugar, se llevó a cabo la reacción de hidroarilación en los metoxialenos β-lactámicos **1**. Debido a la posible formación de al menos dos productos distintos por la competencia existente entre las reacciones de *C*-ciclación frente a las de *O*-ciclación, y a la mayor nucleofilia del átomo de oxígeno respecto al átomo de carbono, el grupo hidroxilo se protegió como éter metílico.[127] Tras llevar a cabo la optimización de condiciones, el tratamiento de estos alenoles *O*-protegidos como éteres metílicos **1** con el catalizador de Gagosz [$Ph_3PAuNTf_2$] en dicloroetano a 110 ºC en microondas, condujo a las benzo[*b*]oxoninas **3** como únicos productos de reacción, a través de una novedosa carbociclación 9-*endo* (Esquema XI.1).

Dicha reacción de hidroarilación alénica tolera diferente sustitución en la posición interna del aleno, ya que los sustratos **1b-h**, que presentan tanto grupos metilo como fenilo en el resto alénico, se transformaron en los productos tricíclicos **3b-h** con rendimientos razonables (Esquema XI.1). Se debe mencionar que el

[127] Para la primera cicloisomerización catalizada por oro de α-alenoles, véase: a) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537. Para referencias concretas, véase: b) Referencia 66.

patrón de sustitución (alquilo frente arilo) en el resto alénico no es una variación trivial, ya que puede provocar grandes cambios en la reactividad.[128]



(+)-**1b** R^1 = isobutilo, R^2 = Me
(+)-**1c** R^1 = isobutilo, R^2 = Ph
(+)-**1d** R^1 = Bn, R^2 = Me
(+)-**1e** R^1 = Bn, R^2 = Ph
(+)-**1f** R^1 = isopropilo, R^2 = Me
(+)-**1g** R^1 = isopropilo, R^2 = Ph
(+)-**1h** R^1 = 2-metilalilo, R^2 = Ph

(+)-**3b** (72%)
(+)-**3c** (60%)
(+)-**3d** (58%)
(+)-**3e** (69%)
(+)-**3f** (65%)
(+)-**3g** (59%)
(+)-**3h** (63%)

Esquema XI.1

El Esquema XI.1 muestra cómo las condiciones suaves de la catálisis de oro permiten la formación quimio y regioselectiva del ciclo de nueve eslabones fusionado al núcleo β-lactámico, manteniéndose la integridad del anillo de cuatro miembros.

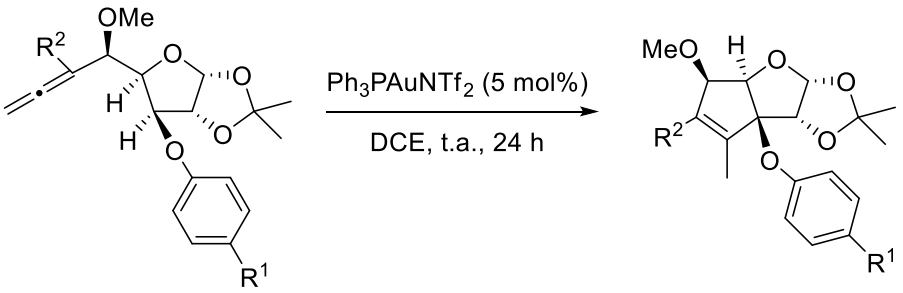
Debido a la importancia de esta nueva reacción de hidroarilación alénica y al gran interés biológico, así como a las atractivas características conformacionales, funcionales y estereoquímicas que presentan los azúcares,[129] decidimos extender esta reactividad a los ariloxialenilazúcares **4**.

Al igual que en los α-alenoles derivados del anillo β-lactámico, antes de llevar a cabo la reacción de hidroarilación deseada, decidimos proteger el grupo hidroxilo de los alenilazúcares **4**, para evitar reacciones de *O*-ciclación. Sorprendentemente, el tratamiento del sustrato **4a** en las mismas condiciones catalíticas ensayadas previamente: $Ph_3PAuNTf_2$ como catalizador y dicloroetano

128 a) Alcaide, B.; Almendros, P.; Carrascosa, R.; Martínez del Campo, T. *Chem. Eur. J.* **2010**, *15*, 13243. b) Alcaide, B.; Almendros, P.; Carrascosa, R.; Martínez del Campo, T. *Chem. Eur. J.* **2009**, *15*, 2496. c) Referencia 66b.

129 a) Suhadolnik, R.J. *Nucleoside Antiobiotics,* Ed. Wiley-Interscience: New York, **1970**. b) Johnson, F. *The Total Synthesis of Natural Products,* Vol 1, Ed. Wiley-Interscience: New York, **1973**.

como disolvente, pero llevando a cabo la reacción a temperatura ambiente, condujo a la formación del ciclopenteno fusionado al núcleo de glucofuranosa **5a**, como único producto de reacción, en lugar de al aducto de hidroarilación de nueve eslabones esperado (Esquema XI.2).



(–)-**4a** R^1 = H, R^2 = Me
(–)-**4b** R^1 = H, R^2 = Et
(–)-**4c** R^1 = H, R^2 = $BnOCH_2$
(–)-**4d** R^1 = Br, R^2 = Me
(–)-**4e** R^1 = Br, R^2 = $BnOCH_2$

(+)-**5a** (46%)
(+)-**5b** (34%)
(+)-**5c** (48%)
(+)-**5d** (35%)
(+)-**5e** (41%)

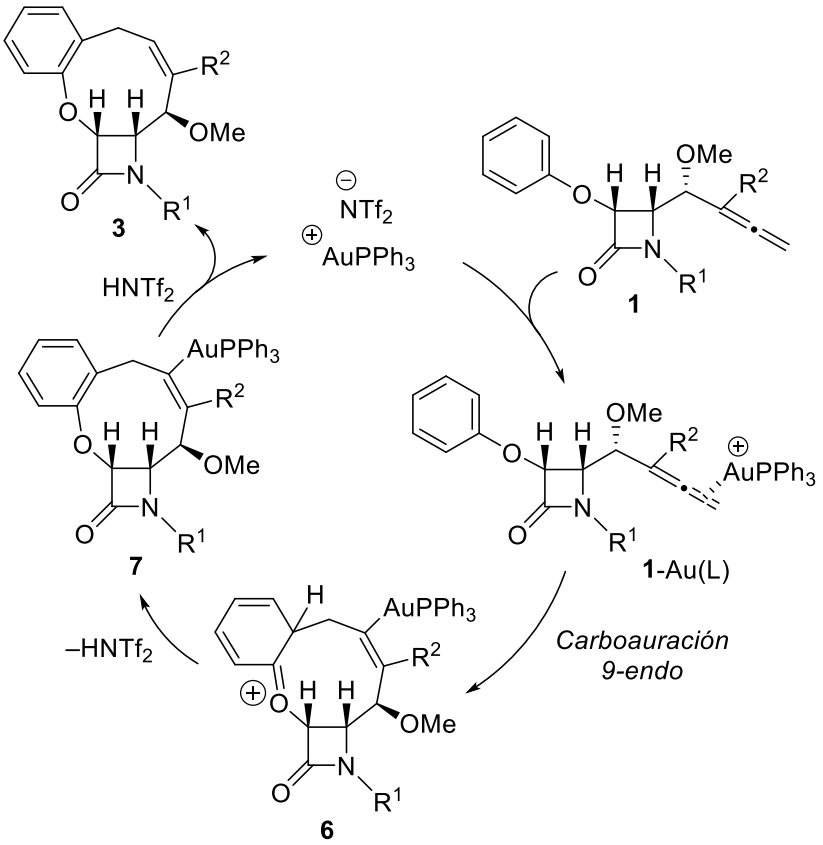
Esquema XI.2

Aunque este resultado no era el deseado inicialmente, presenta gran relevancia ya que constituye uno de los primeros ejemplos de reactividad de alenilazúcares en reacciones catalizadas por metales de transición. Además, el núcleo de 2*H*-ciclopenta[*b*]furano obtenido está presente en heliconoles, productos naturales biológicamente activos.[130]

Por todo ello, decidimos estudiar el alcance de esta nueva reacción de ciclación catalizada por oro en los alenilazúcares **4a-e**, que presentaban diferente sustitución tanto en el aleno como en el grupo aromático, obteniéndose los productos **5** con rendimientos razonables a través de una hidroalquilación 5-*exo* poco común (Esquema XI.2). La reacción transcurre de forma totalmente estereoselectiva, representando así un método muy eficaz para la formación de ciclopentenos fusionados con un centro cuaternario en su estructura, a través de la funcionalización de un enlace, de otra manera inactivo, C_{sp3}–H.

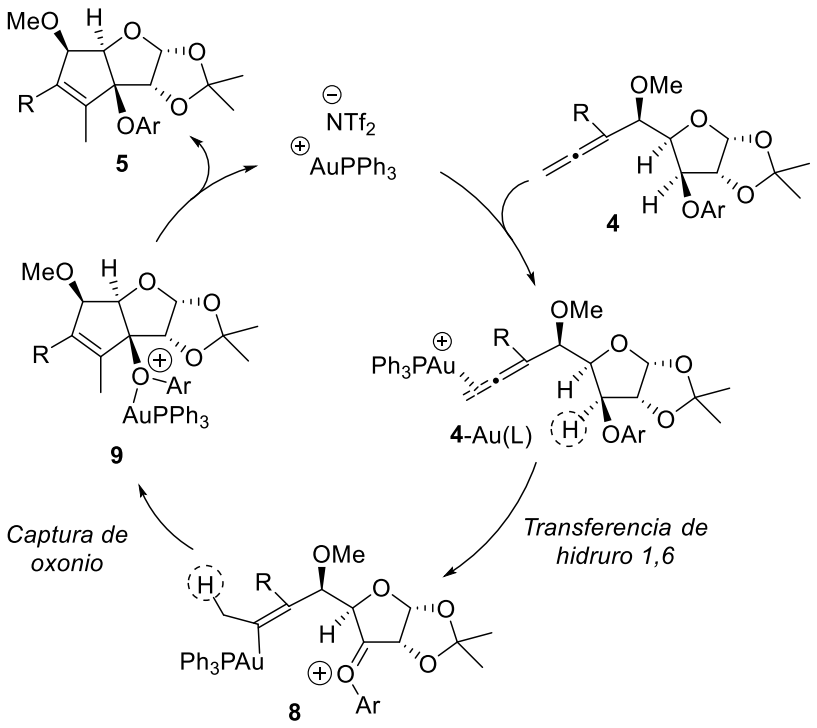
130 Mudur, S.V.; Swenson, D. C.; Gloer, J. B.; Campbell, J.; Shearer, C. A. *Org. Lett*. **2006**, *8*, 3191.

La reactividad divergente observada en estos ariloxialenos **1** y **4**, funcionalización C_{sp2}–H frente a C_{sp3}–H, puede explicarse a través de los mecanismos propuestos para cada una de las reacciones (apoyados por cálculos DFT). Así, mientras la formación de los triciclos **3** implicaría una carboauración 9-*endo*, resultante del ataque nucleófilo por la posición 2 del areno al sustituyente alénico activado por el oro (Esquema XI.3); en la formación de los ciclopentenos **5** se produciría una transferencia de hidruro 1,6,[131] en lugar del ataque usual del grupo nucleófilo, seguida de la captura intramolecular del grupo oxonio por el sustituyente alquenil-oro, a través de una hidroalquilación 5-*exo* (Esquema XI.4).



Esquema XI.3

131 Para una transferencia de hidruro 1,5 desde bencil-éteres y tetrahidrofuranos a alenos, véase: Bolte, B.; Gagosz, F. *J. Am. Chem. Soc.* **2011**, *133*, 7696.



Esquema XI.4

Por último, se debe mencionar que los triciclos fusionados **3** contienen el núcleo de éter fenólico cíclico de nueve miembros que aparece en muchos productos naturales tales como la fomopsina A. [132] Adicionalmente estos compuestos poseen un anillo β-lactámico que, además de ser un intermedio sintético versátil, como se ha comentado anteriormente, es el motivo estructural clave en compuestos biológicamente relevantes, tales como antibióticos o inhibidores de enzimas.[133]

Por este motivo decidimos estudiar la actividad citotóxica de dos de los productos obtenidos en este proyecto, los compuestos (+)-**3b** y (+)-**3c**, frente a la línea celular HL-60 de leucemia promielocítica humana, adquirida a la American Type Culture Collection (ATCC), y mantenida en medio RPMI1640, junto a glutamina (2mM), penicilina (50 IU/mL), estreptomicina (50 g/mL), anfotericina (1.25 g/mL) y suplementada con un 20% de suero fetal bovino.

Los valores de IC50, entendida ésta como la concentración de compuesto que presenta un 50% de la supervivencia celular de control sin tratar, de los

132 Huang, Z.; Cai, X.; Shao, C.; She, Z.; Xia, X.; Chen, Y.; Yang, J.; Zhou, S.; Lin, Y. *Phytochemistry* **2008**, *69*, 1604.

133 Para la importancia biológica de β-lactamas véanse referencias 6, 71, 73, 74 y 75.

benzociclos fusionados de nueve miembros se determinaron utilizando el ensayo colorimétrico de Mossman (Tabla XI.1).[134]

Compuesto	IC50 (μL/mL)
(+)-**3b**	29
(+)-**3c**	22

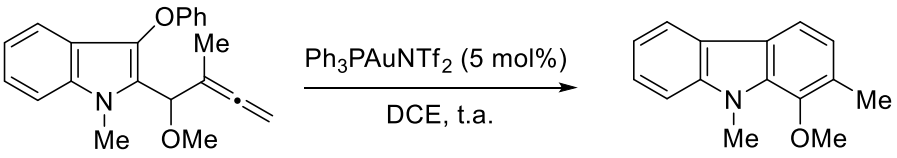
Tabla XI.1. Actividad citotóxica de los compuestos (+)-**3b** y (+)-**3c**.

A la vista de estos resultados se observó que ambos compuestos mostraban una cierta citotoxicidad frente a la línea celular HL-60 de leucemia ensayada; confirmándose de esta forma la actividad biológica de los triciclos obtenidos.

XI.1.2. Capítulo 2: Transposición de yodo catalizada por metales a través de una migración 1,3 en yodoindoles

Una vez explorada la reactividad de ariloxialenos unidos al núcleo de β-lactama y al anillo de glucofuranosa (Capítulo 1), decidimos extender el estudio de esta reacción de carbociclación catalizada por oro en ariloxialenil-indoles.

En nuestro estudio inicial escogimos como sustrato modelo el 3-fenoxi-2-alenil-indol metilsustituido protegido como éter metílico **13b**, y las condiciones previamente optimizadas: $Ph_3PAuNTf_2$ como catalizador y dicloroetano como disolvente, llevando a cabo la reacción a temperatura ambiente. De esta forma, observamos la formación del 1-metoxicarbazol **19b** como único producto de reacción con buen rendimiento (Esquema XI.5).



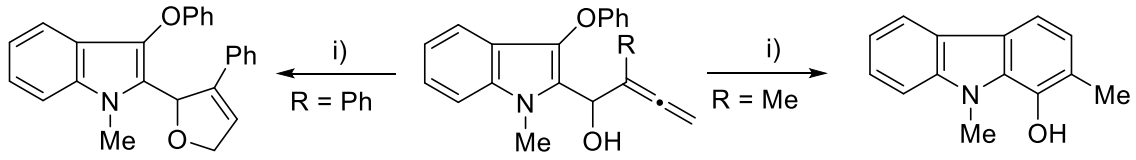
13b **19b** (51%)

Esquema XI.5

134 Mosmann, T. *J. Immunol. Methods.* **1983**, *65*, 55.

Este resultado presenta un gran atractivo ya que en la literatura no existen ejemplos de formación de carbazoles a partir de alenil-indoles que mantengan el grupo oxigenado en C1, como sucede en nuestro ensayo. Asimismo se debe mencionar que los carbazoles 1-oxifuncionalizados son de un gran interés debido a que presentan citotoxicidad frente a líneas celulares de cáncer.[135]

Por tanto, a la vista de este resultado, decidimos extender esta metodología de preparación de 1-oxicarbazoles a diferentes alenoles que presentaran el grupo hidroxilo libre. Así, se estudió la reactividad del alenol **13a** no protegido como éter metílico utilizando las mismas condiciones de reacción. Afortunadamente, el tratamiento de este alcohol α-alénico condujo al 1-hidroxicarbazol **19a**, confirmándose así la carbociclación 6-*endo* seguida de eliminación de fenol como modo operativo de la ciclación (Esquema XI.6).



14c (46%) **13a** R = Me **13c** R = Ph **19a** (57%)

i) $(Ph_3P)AuNTf_2$ (5 mol%), DCE, t.a.

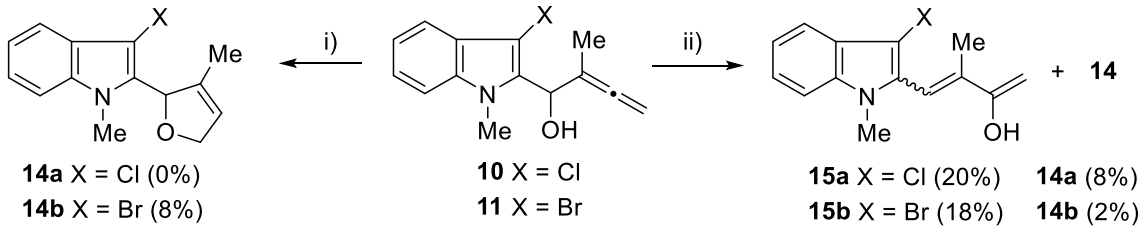
Esquema XI.6

Animados por este resultado, decidimos estudiar el alcance de la reacción de carbociclación en el alenil-indol **13c**, que presentaba un grupo fenilo en la posición interna del aleno. El tratamiento de éste en las mismas condiciones de reacción no condujo a la formación del 1-hidroxicarbazol esperado, obteniéndose por el contrario el 2,5-dihidrofurano **14c** como único producto de reacción. El cambio del sustituyente alquilo por arilo provoca modificaciones en la densidad electrónica del aleno, así como un incremento en el impedimento estérico, lo que podría justificar la preferencia de la oxiciclación 5-*endo*, en lugar de la

135 Todos los alcaloides carbazólicos 1-oxifuncionalizados aislados hasta la fecha provienen de plantas superiores. El género de árbol Murraya (familia Rutaceae) que crece en el sur de Asia representa la mayor fuente de alcaloides del tipo 1-oxicarbazol. Para una revisión reciente véase: Schimidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193.

carbociclación 6-*endo* deseada (Esquema XI.6). Con el fin de evitar la *O*-ciclación, decidimos proteger el alenol **13c** como éter metílico. Sin embargo, resultó imposible su protección; por lo que no se pudo explorar finalmente su reactividad.

En este punto nos planteamos explorar la reactividad de alenil-indoles que presentaran un sustituyente diferente en la posición C3, cambiando el grupo fenoxi por un átomo de hálogeno. Para ello, se llevó a cabo el tratamiento de los alenoles **10** y **11**, con un átomo de cloro y bromo respectivamente, en las condiciones previamente optimizadas de catálisis de oro. Desafortunadamente, la reacción de carbociclación no tuvo lugar obteniéndose una mezcla de los dihidrofuranos **14** y los dienos **15** con bajos rendimientos (Esquema XI.7). La catálisis de paladio tampoco mejoró los resultados obtenidos conduciendo únicamente a la reacción de oxiciclación, usualmente más favorecida (Esquema XI.7).[136]



14a X = Cl (0%)
14b X = Br (8%)

10 X = Cl
11 X = Br

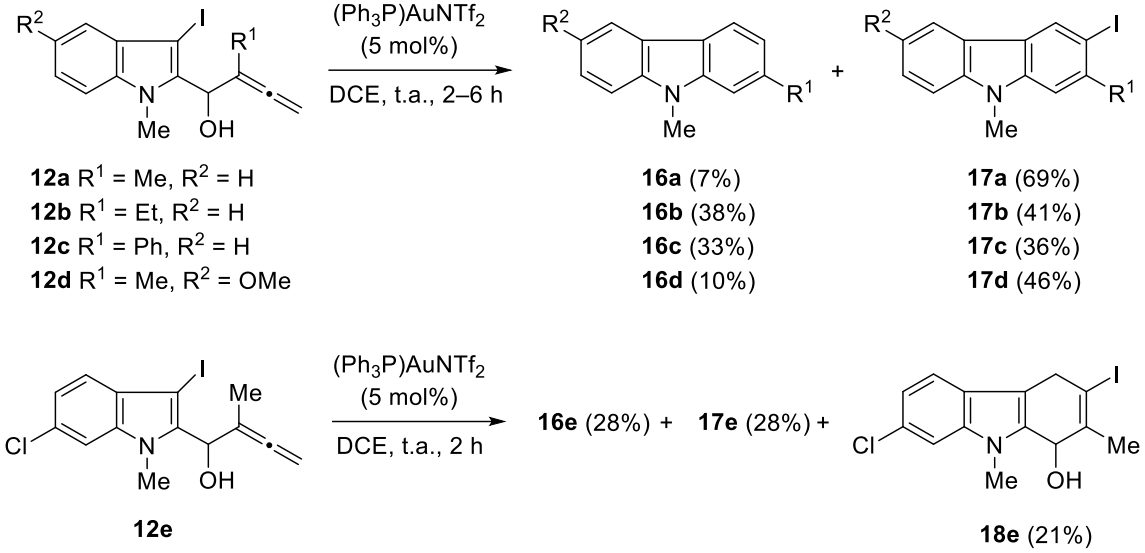
15a X = Cl (20%) **14a** (8%)
15b X = Br (18%) **14b** (2%)

i) $(Ph_3P)_2PdCl_2$ (5 mol%), DMF, t.a., 2h
ii) $(Ph_3P)AuNTf_2$ (5 mol%), DCE, t.a., 20h

Esquema XI.7

A la vista de este resultado decidimos estudiar la incorporación de un átomo de yodo, en lugar de bromo o cloro, en la posición C3 del alenilindol de partida. Afortunadamente, el tratamiento de los 3-yodoalenil-indoles **12**, que presentaban diferentes grupos en el carbono interno del aleno así como distinta sustitución en las posiciones C5 y C6 del indol, tanto grupos electroatractores como electrodadores, en las mismas condiciones de catálisis de oro, condujo a una mezcla separable de los carbazoles **16** y los yodocarbazoles **17** (Esquema XI.8).

136 Ma. S. *Chem. Rev.* **2005**, *105*, 2829.

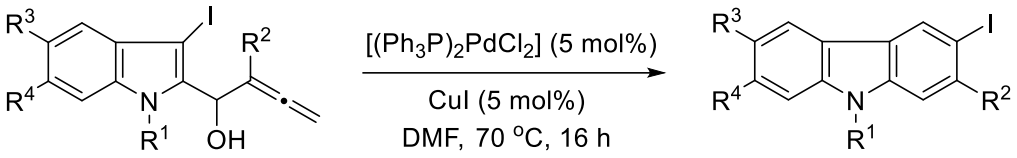


Esquema XI.8

La obtención de los yodocarbazoles **17** supone un gran reto en Síntesis Orgánica ya que el átomo de halógeno procedente de los yodoalenil-indoles de partida se incorpora al producto final en lugar de ser eliminado,[137] como suele ocurrir en las reacciones de haluros de arilo catalizadas por metales.[138]

Asimismo, los yodocarbazoles **17** representan intermedios muy interesantes considerando la versatilidad que exhiben los compuestos yodados en las transformaciones químicas.[139] Por ello, decidimos aumentar la eficiencia de la reacción de yodocarbociclación estudiando otros sistemas catalíticos diferentes. El mejor resultado se obtuvo para el sistema bimetálico $PdCl_2(PPh_3)_2$/CuI en DMF, dando lugar de forma exclusiva a los 3-yodocarbazoles **17** con buenos rendimientos (Esquema XI.9). Desafortunadamente, los sustratos fenilsustituidos **12c** y **12g** no se transformaron en los correspondientes yodocarbazoles debido posiblemente al incremento del impedimento estérico así como a la interacción π del sistema aromático con el centro metálico.

137 Para una revision véase: Schomaker, J. M.; Grigg, R. D.; *Synlett,* **2013**, 401.
138 Chinchilla, R.; Nájera, Eds. C. *Chem. Soc. Rev.* **2011**, *40*, issue 10.
139 a) Li, J.; Grimsdale, A. C. *Chem. Soc. Rev.* **2010**, *39*, 2399. b) Véase referencia 135.



12a R^1 = Me, R^2 = Me, R^3 = R^4 = H — **17a** (61%)
12c R^1 = Me, R^2 = Ph, R^3 = R^4 = H — **17c** (0%)
12e R^1 = Me, R^2 = Me, R^3 = H, R^4 = Cl — **17e** (50%)
12f R^1 = H, R^2 = Me, R^3 = R^4 = H — **17f** (52%)
12g R^1 = H, R^2 = Ph, R^3 = R^4 = H — **17g** (0%)
12h R^1 = H, R^2 = Me, R^3 = OMe, R^4 = H — **17h** (75%)

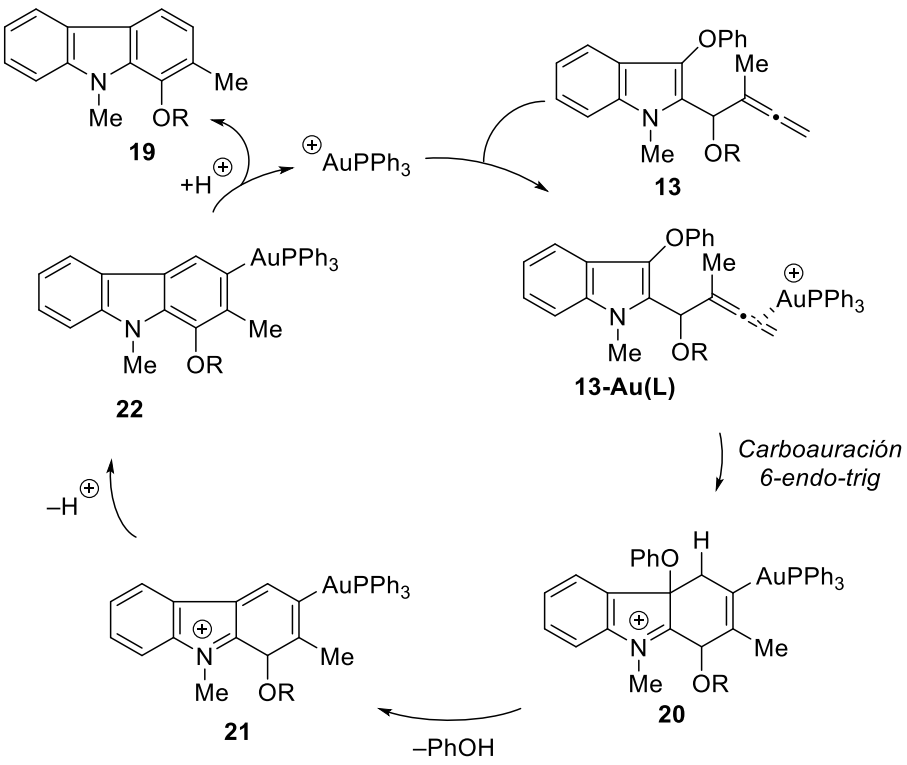
Esquema XI.9

Esta reacción, tanto catalizada por oro como por paladio, presenta una alta economía atómica y puede considerarse como un ejemplo novedoso de reciclado de yodo a través de una migración intramolecular 1,3 del átomo de halógeno.[140]

Tanto la formación de los 1-oxicarbazoles **19** como la de los 3-yodocarbazoles **17**, implicaría una carbociclación 6-*endo-trig* quimio- y regioselectiva, resultante del ataque nucleófilo de la posición C3 del indol como consecuencia de la estabilidad del catión imínico formado en ambos casos (Esquema XI.10 y Figura XI.1). Sin embargo, en este punto el intermedio **20**, derivado de los 3-fenoxialenil-indoles **13** sufriría una eliminación de fenol (Esquema XI),[141] mientras que en el intermedio **INT2**, derivado de los 3-yodoalenil-indoles **12**, tendría lugar una migración 1,3 de yodo al doble enlace endocíclico del anillo de seis miembros adyacente (Figura XI.1). Este último proceso, apoyado por cálculos DFT y que se asemeja a la típica adición electrófila de halógenos a alquenos, representa una adición intramolecular sin precedentes del catión yodonio a un doble enlace activado por un metal.

140 a) Grigg, R. D.; Van Hoveln, R.; Schomaker, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 16131. b) Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 1778. C) Nösel, P.; Lauterbach, T.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Chem. Eur. J.* **2013**, *19*, 8634.

141 a) Hashmi, A S. K.; Yang, W.; Rominger, F. *Angew. Chem. Int. Ed*. **2011**, *50*, 5762; b) Hashmi, A. S. K.; Wölfle, M. *Tetrahedron*, **2009**, *65*, 9021.



Esquema XI.10

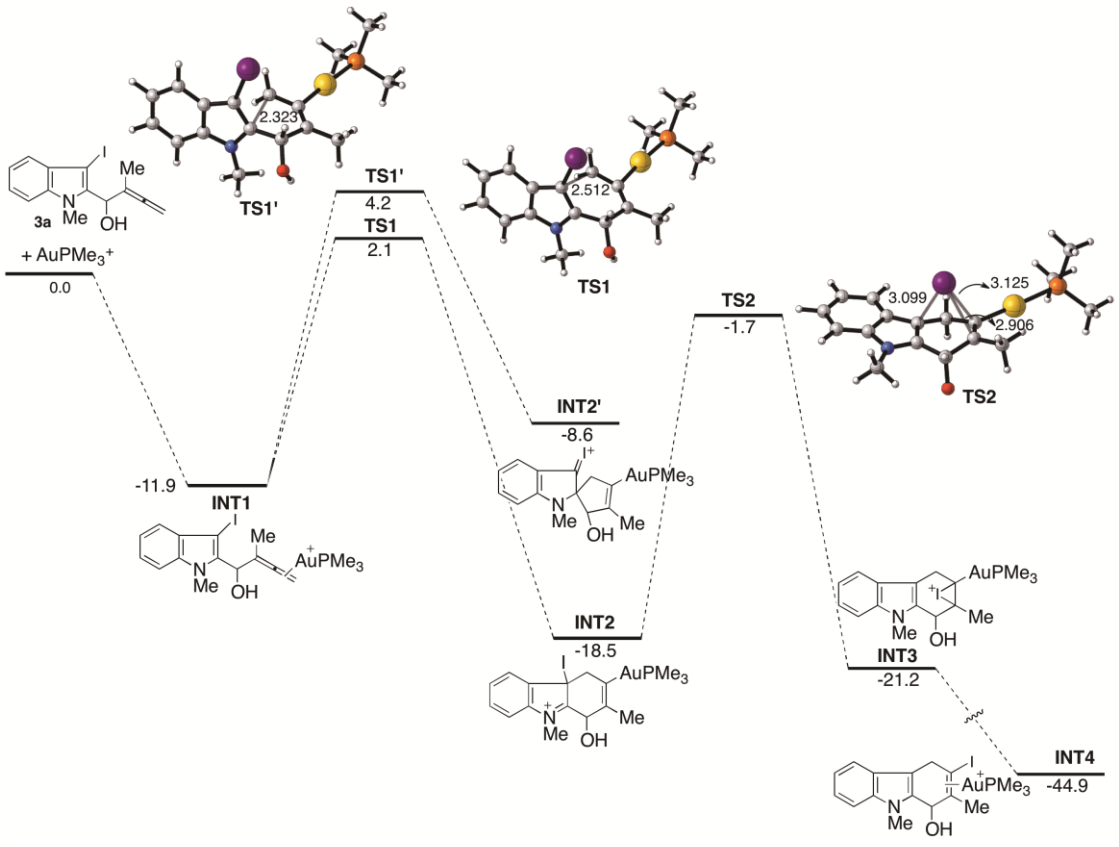


Figura XI.1

Finalmente, los cálculos DFT realizados demostraron que las barreras de activación calculadas para los desplazamientos 1,3 de halógeno en el caso de los átomos de cloro y bromo son mucho más altas que la barrera de activación correspondiente al átomo de yodo (Figura XI.2), por lo que la aptitud migratoria de los átomos de halógeno en los procesos catalizados por metales de transición seguiría el siguiente orden: I >> Br > Cl; lo que concuerda con los resultados obtenidos de forma experimental.[142]

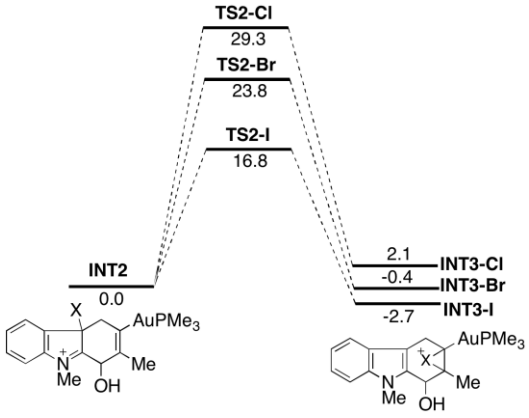


Figura XI.2

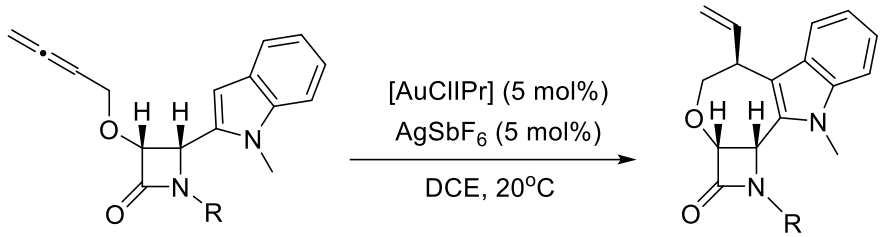
XI.1.3. Capítulo 3: El oro como catalizador para la hidroarilación y el proceso dominó hidroarilación/ruptura N1-C4 de alenilindoles unidos a β-lactamas

Una vez explorada la reacción de carbociclación catalizada por oro en alenos unidos al anillo de 2-azetidinona (Capítulo 1) y al núcleo de indol (Capítulo 2), nos propusimos como nuevo objetivo el estudio de esta reacción en alenos que presentaran ambos núcleos en la misma estructura.

Para ello, se escogieron en primer lugar los compuestos **27**, que presentaban un anillo β-lactámico unido a un sustituyente alénico por la posición C3 y a un núcleo de indol por C4. El tratamiento de estos alenil-indoles unidos a β-lactama **27a-e**, sustituidos tanto con grupos alquilo como arilo en el nitrógeno β-lactámico, en las condiciones de catálisis de oro ya optimizadas, [AuClIPr]/$AgSbF_6$ (proporción 1:1) en dicloroetano a temperatura ambiente, condujo a los

142 Una tendencia similar se ha observado en las reacciones 1,2-diotrópicas, véase: a) Fernández, I.; Bickelhaupt, F. M.; Cossío, F. P. *Chem. Eur. J*. **2012**, *18*, 12395. Para una revisión reciente de reacciones 1,2 diotrópicas, véase b) Fernández, I.; Cossío, F. P.; Sierra, M. A. *Chem. Rev*. **2009**, *109*, 6687.

compuestos tetracíclicos **29a-e** como únicos productos de reacción con buenos rendimientos, a través de una carbociclación 7-*exo* quimio, regio y esteroselectiva (Esquema XI.11).



27a R = Bn
27b R = PMB
27c R = PMP
27d R = PBrB
27e R = isobutilo

29a R = Bn (72%)
29b R = PMB (68%)
29c R = PMP (63%)
29d R = PBrB (82%)
29e R = isobutilo (89%)

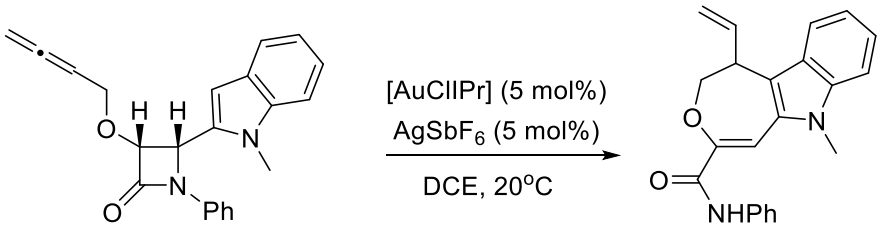
29a: 5h; **29b:** 4.5 h; **29c:** 2.5 h; **29d:** 6.5 h; **29e:** 2 h.

Esquema XI.11

Los tetraciclos formados **29** reúnen en la misma estructura tres núcleos de gran importancia biológica, como son el anillo de 2-azetidinona, el ciclo de oxepano y el núcleo de indol, lo que les confiere gran interés ya que son numerosos los compuestos tricíclicos fusionados al anillo del indol que exhiben actividad biológica, estando presentes en numerosos productos naturales y fármacos sintéticos.[143]

Sorprendentemente, cuando llevamos a cabo la misma reacción en el alenil-indol **27f**, que presentaba un grupo fenilo unido a la posición N1 del anillo β-lactámico, observamos la formación de un producto diferente, el compuesto **30f**, cuya estructura no contenía el núcleo de 2-azetidinona (Esquema XI.12).

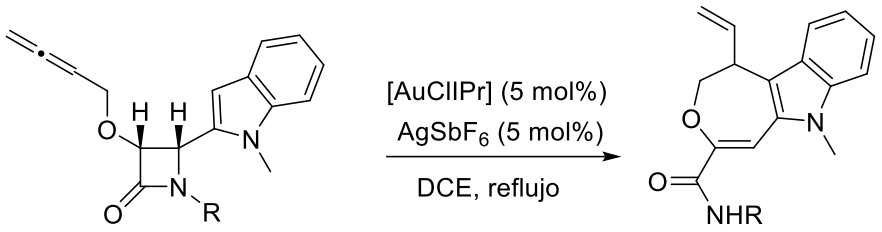
143 a) Andriantsiferana, M.; Besselievre, R.; Riche, C.; Husson, H. P. *Tetrahedron Lett.* **1977**, *30*, 2587. b) Smitka, T. A.; Bonjouklian, R.; Doolin, L.; Jones, N. D.; Deeter, J. B.; Yoshida, W. Y.; Prinsep, M. R.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1992**, *57*, 857. c) Carrol, A. R.; Hyde, E.; Smith, J.; Quinn, R. J.; Guymer, G.; Foster, P. I. *J. Org. Chem.* **2005**, *70*, 1096. d) Zhang, H.; Yue, J.-M. *Helv. Chim. Acta* **2005**, *88*, 2537. e) Raveh, A.; Carmeli, S. *J. Nat. Prod.* **2007**, *70*, 196. f) Barf, T.; Lehmann, F.; Hammer, K.; Haile, S.; Axen, E.; Medina, C.; Uppenberg, J.; Svensson, S.; Rondahl, L.; Lundbaeck, T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1745. g) Mo, S.; Krunic, A.; Chlipala, G.; Orjala, J. *J. Nat. Prod.* **2009**, *72*, 894. h) Mo, S.; Krunic, A.; Santarsiero, B. D.; Franzblau, S. G.; Orjala, J. *Phytochemistry* **2010**, *71*, 2116. i) Zhang, Q.; Mándi, A.; Li, S.; Chen, Y.; Zhang, W.; Tian, X.; Zhang, H.; Li, H.; Zhang, W.; Zhang, S.; Ju, J.; Kurtán, T.; Zhang, C. *Eur. J. Org. Chem.* **2012**, 5256. j) Sarkar, S.; Bera, K.; Jana, U. *Tetrahedron Lett.* **2014**, *55*, 6188. El sustituyente oxepano fusionado a un grupo arilo también está presente en moléculas bioactivas: k) Reekie, T. A.; Kavanagh, M. E.; Longworth, M.; Kassiou, M. *Synthesis* **2013**, 3211.



27f **30f** (98%)

Esquema XI.12

A la vista de este resultado, y con el fin de estudiar si esta nueva metodología era aplicable a los alenos previamente estudiados **27**, decidimos optimizar unas nuevas condiciones de reacción. Afortunadamente, cuando se llevó a cabo la reacción en las mismas condiciones catalíticas y el mismo disolvente pero a temperatura de reflujo (85 ºC para el dicloroetano), se obtuvieron los aductos **30** con total selectividad y buenos rendimientos (Esquema XI.13).



27a R = Bn
27b R = PMB
27c R = PMP
27d R = PBrB
27e R = isobutilo

30a R = Bn (60%)
30b R = PMB (53%)
30c R = PMP (67%)
30d R = PBrB (40%)
30e R = isobutilo (58%)

30a: 2 h; **30b:** 2.5 h; **30c:** 2 h; **30d:** 4 h; **30e:** 1.5 h; **30f:** 1.5 h.

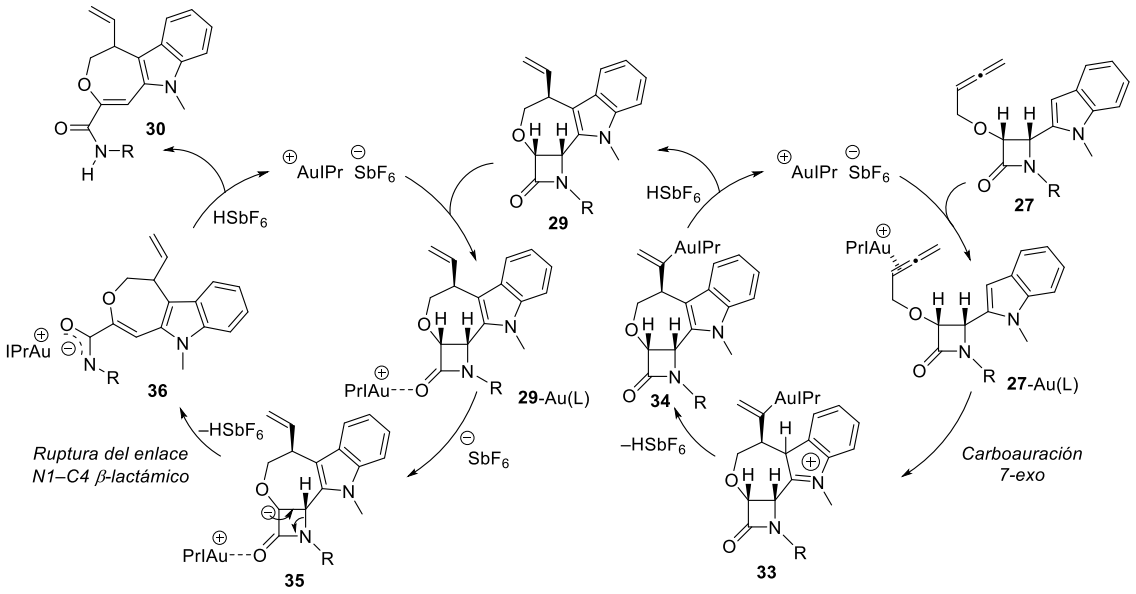
Esquema XI.13

La formación de los oxepino-indoles **30** implica la ruptura selectiva del enlace N1–C4 del núcleo de 2-azetidinona, nunca antes descrita en la literatura a través de catálisis metálica.[144] Asimismo, la reacción de hidroarilación seguida de ruptura del enlace N1–C4 β-lactámico, representa una herramienta útil para la construcción de α-hidroxiamidas indólicas.

144 Para una revisión de la ruptura selectiva de los enlaces del anillo β-lactámico véase: Referencia 7c.

Con el fin de averiguar si las carboxamidas tricíclicas **30** pueden formarse a partir de los tetraciclos **29** en ausencia de catálisis metálica, llevamos a cabo el tratamiento del compuesto **29a** en dicloroetano a reflujo durante 3 horas. La reacción no tuvo lugar sin el empleo del catalizador. Por el contrario, la reacción de **29a** en presencia de [IPrAuSbF$_6$] en similares condiciones de reacción dio lugar al triciclo **30a** con un rendimiento excelente, confirmando así el papel decisivo de la sal de oro en la ruptura del enlace N1–C4 β-lactámico.

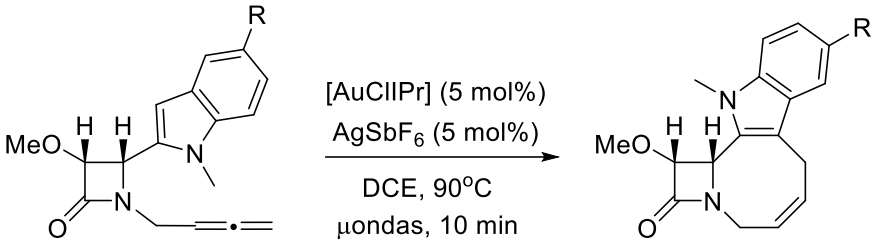
Este resultado muestra que la formación de los compuestos **30** tiene lugar a través de los tetraciclos **29** como intermedios en el mecanismo propuesto en el Esquema XI.14 (ciclo catalítico de la izquierda). La formación de estos últimos, por su parte, implicaría una carbociclación 7-*exo*-*trig* quimio- y regioselectiva, resultante del ataque nucleófilo de la posición C3 del indol como consecuencia de la estabilidad del catión intermedio iminio formado (Esquema XI.14, ciclo catalítico de la derecha).



Esquema XI.14

A la vista de los interesantes resultados obtenidos, decidimos estudiar el alcance de esta reacción con el tratamiento de los alenil-indoles **28**, en los que el sustituyente alénico se encuentra unido al átomo de nitrógeno en lugar de a la posición C3 del anillo β-lactámico, utilizando las mismas condiciones de catálisis de oro.

La reacción de carbociclación de los compuestos **28a-c**, que presentaban tanto grupos electrodadores como electroatractores unidos al núcleo indólico, no tuvo lugar a temperatura ambiente. Afortunadamente, la aplicación de microondas a 90 ºC condujo a los tetraciclos **31a-c** como únicos isómeros, a través de una carbociclación 8-*endo*, tras diez minutos de reacción (Esquema XI.15).

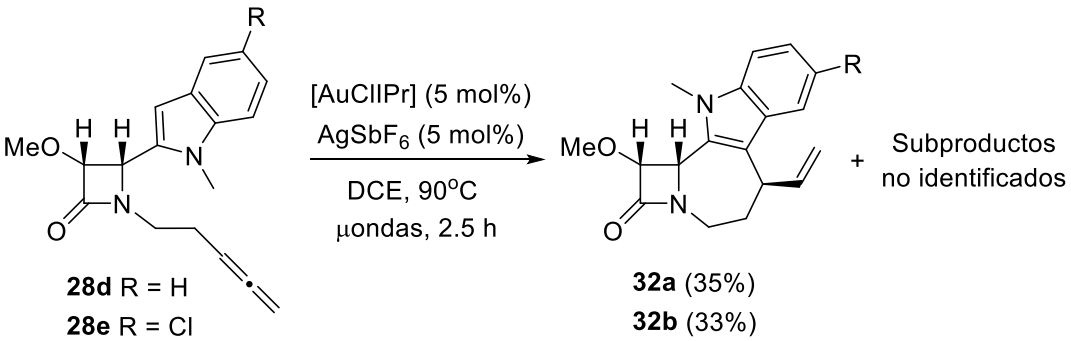


28a R = H
28b R = Cl
28c R = OMe

31a (59%)
31b (70%)
31c (53%)

Esquema XI.15

Por su parte, la reacción de los alenil-indoles unidos a β-lactama **28d-f**, que presentaban un eslabón más en la cadena alifática entre el aleno y el anillo de 2-azetidinona que sus homólogos, los compuestos **28a-c**, dio lugar a los tetraciclos **32a-c** como isómeros mayoritarios (Esquema XI.16). La reacción transcurrió a través de una carbociclación 7-*exo*, resultante del ataque nucleófilo de la posición C2 del indol al carbono interno del aleno, observándose así un cambio en la regioselectividad del proceso frente a la carbociclación 8-*endo* de sus homólogos inferiores. Por el análisis de ^{1}H-RMN del crudo de reacción se observó la formación de algunos productos minoritarios, no identificados, responsables del bajo rendimiento obtenido en los productos finales.



28d R = H
28e R = Cl
28f R = OMe

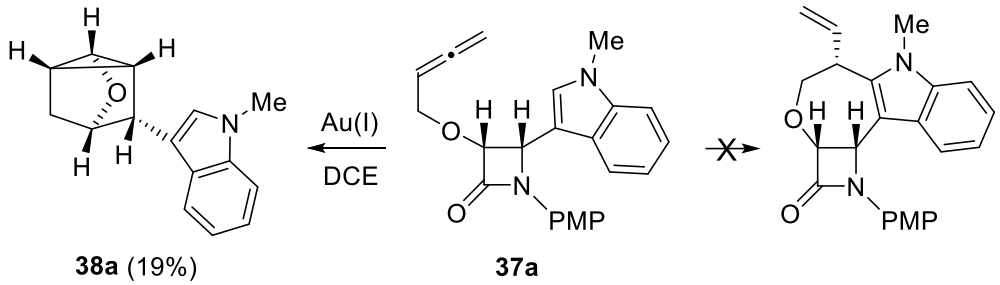
32a (35%)
32b (33%)
32c (36%)

Esquema XI.16

XI.1.4. Síntesis estereoselectiva de compuestos tensionados “tipo caja” mediante funcionalización de alenil-β-lactamas catalizada por oro

Una vez explorada la reacción de carbociclación catalizada por oro en las alenil-β-lactamas **27**, unidas al núcleo de indol por su posición C2 (Capítulo 3), decidimos abordar el estudio de esta reacción en alenil-β-lactamas en las que la unión entre el anillo de 2-azetidinona y el indol se produjera por la posición C3 del núcleo indólico.

Para ello, se escogió como sustrato modelo la alenil-β-lactama **37a** y se aplicaron las condiciones previamente optimizadas para la formación de los compuestos **29** (Capítulo 3). Sorprendentemente, el tratamiento del sustrato **37a** con el sistema catalítico [AuIPrCl]/$AgSbF_6$ en dicloroetano a temperatura ambiente condujo, en lugar de al aducto de hidroarilación esperado, al compuesto **38a**, que presentaba una compleja estructura “tipo caja” en la que el anillo de 2-azetidinona había desparecido (Esquema XI.17).

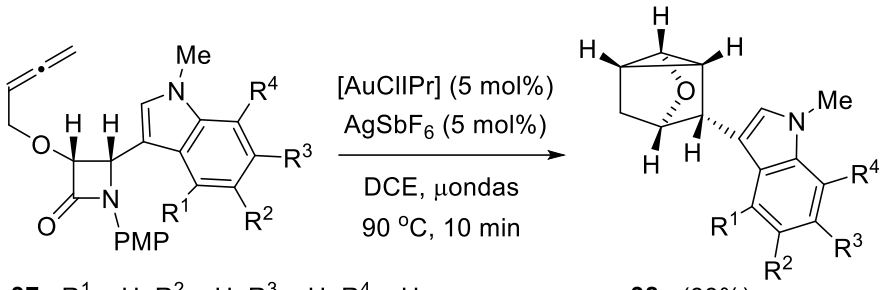


38a (19%) **37a**

Esquema XI.17

El aumento de la temperatura a 90 ºC y la aplicación de microondas, utilizando el mismo sistema catalítico [AuIPrCl]/$AgSbF_6$ en dicloroetano, mejoró el rendimiento del compuesto **38a** hasta un 83%. Una vez optimizadas las condiciones de reacción, decidimos estudiar su alcance en las alenil-4-indolil β-lactamas **37b-f**. Examinando la influencia de la sustitución aromática en el anillo de indol, se encontró que los sustratos **37a-f**, que presentaban tanto grupos electroatractores como grupos electrodadores unidos a cualquiera de las posiciones del anillo de seis miembros del núcleo indólico, se transformaron en los compuestos caja **38a-f** como únicos productos de reacción con buenos

rendimientos (Esquema XI.18). La reacción transcurrió de forma totalmente estereoselectiva, creándose cinco centros estereogénicos contiguos en una sola operación.



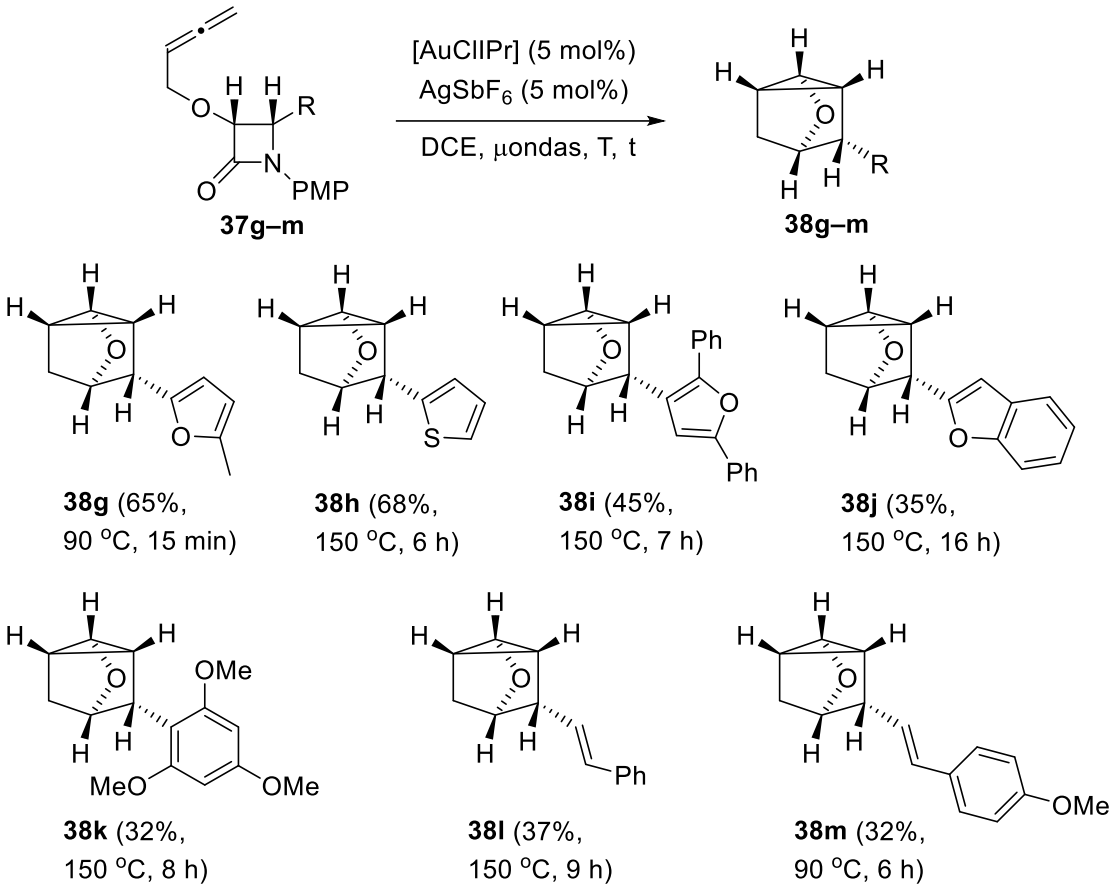
37a R^1 = H, R^2 = H, R^3 = H, R^4 = H — **38a** (83%)
37b R^1 = H, R^2 = Br, R^3 = H, R^4 = H — **38b** (64%)
37c R^1 = NO_2, R^2 = H, R^3 = H, R^4 = H — **38c** (85%)
37d R^1 = H, R^2 = MeO, R^3 = H, R^4 = H — **38d** (74%)
37e R^1 = H, R^2 = H, R^3 = H, R^4 = Me — **38e** (57%)
37f R^1 = H, R^2 = H, R^3 = iPr, R^4 = H — **38f** (60%)

Esquema XI.18

Debido al atractivo que presentan estos nuevos compuestos tensionados tipo caja gracias a sus formas y simetrías poco comunes,[145] decidimos extender esta nueva metodología a alenil β-lactamas diferentemente sustituídas en la posición C4 del anillo de 2-azetidinona.

Así, en nuestro estudio por determinar el alcance de la reacción, descubrimos que las alenil-β-lactamas de partida **37** podían presentar, además del anillo de indol previamente estudiado, un gran número de sustituyentes arilo, heteroarilo y alquenilo unidos al anillo β-lactámico, ya que el tratamiento de los alenos **37g-m**, en las condiciones previamente optimizadas, condujo a los compuestos **38g-m** como únicos productos de reacción (Esquema XI.19). Asimismo, se determinó que la naturaleza electrónica de estos sustituyentes presentaba una gran influencia en la reacción, no siendo compatibles los grupos electroatractores, como el 4-nitrofenil o los heterociclos π-deficientes como la piridina.

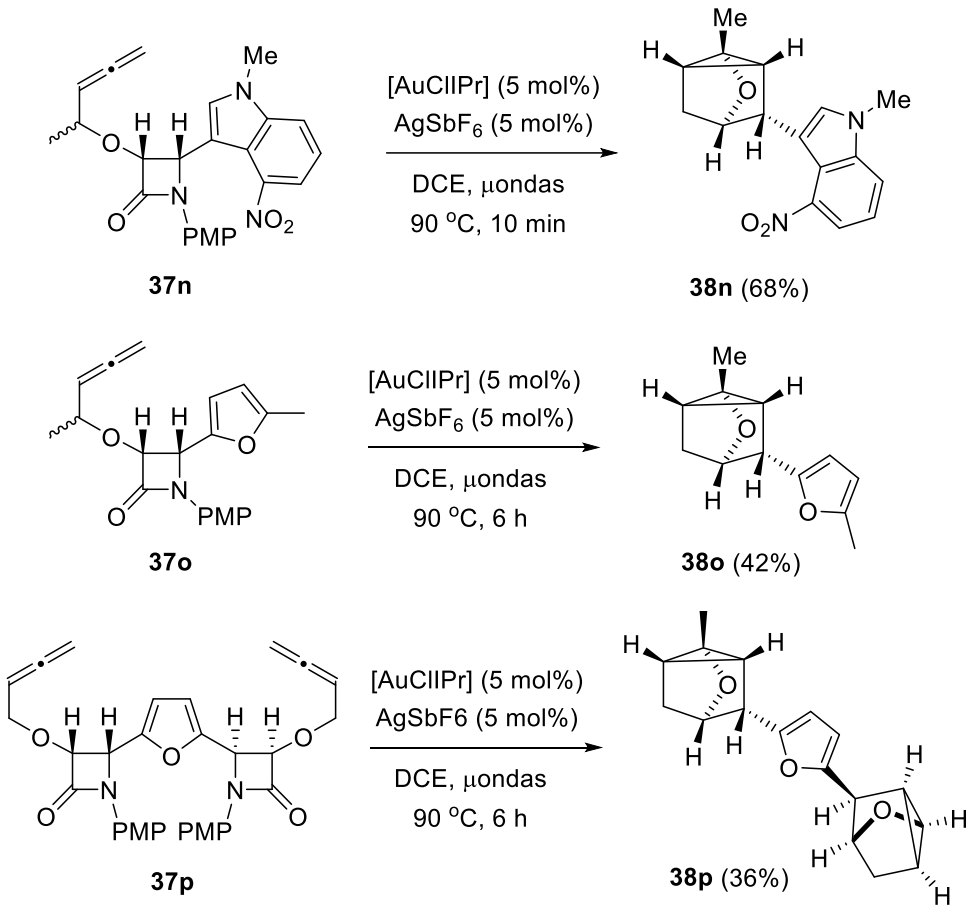
145 a) Wu, H.–J. *Advances in Strained and Interesting Organic Molecules Supplement 1: Carbocyclic and Heterocyclic Cage Compounds and Their Building Blocks*, ed. K. K. Laali, JAI Press, Stamford, CT, 1999, p. 167. Asimismo, se han preparado dos oxatricicloheptanos relacionados a través de un cicloisomerización catalizada por oro de 1,6-eninos: b) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306.



Esquema XI.19

Posteriormente se estudió la influencia en la variación del sustituyente unido a la posición C3 del anillo β-lactámico, utilizando para ello los alenos metilsustituidos **37n** y **37o**. Afortunadamente, ambos se transformaron en los compuestos caja **38n** y **38o** con rendimientos moderados (Esquema XI.20). Cabe mencionar que, aun partiendo de una mezcla de epímeros, en ambos casos se obtuvo un único isómero del producto final; lo que confirma que la reacción estudiada no necesita la preparación estereoselectiva de los materiales de partida.

Finalmente, probamos nuestras condiciones de reacción en la bis(alenil-β-lactama) **37p**, obteniendo el producto caja doble **38p** de forma totalmente selectiva (Esquema XI.20).



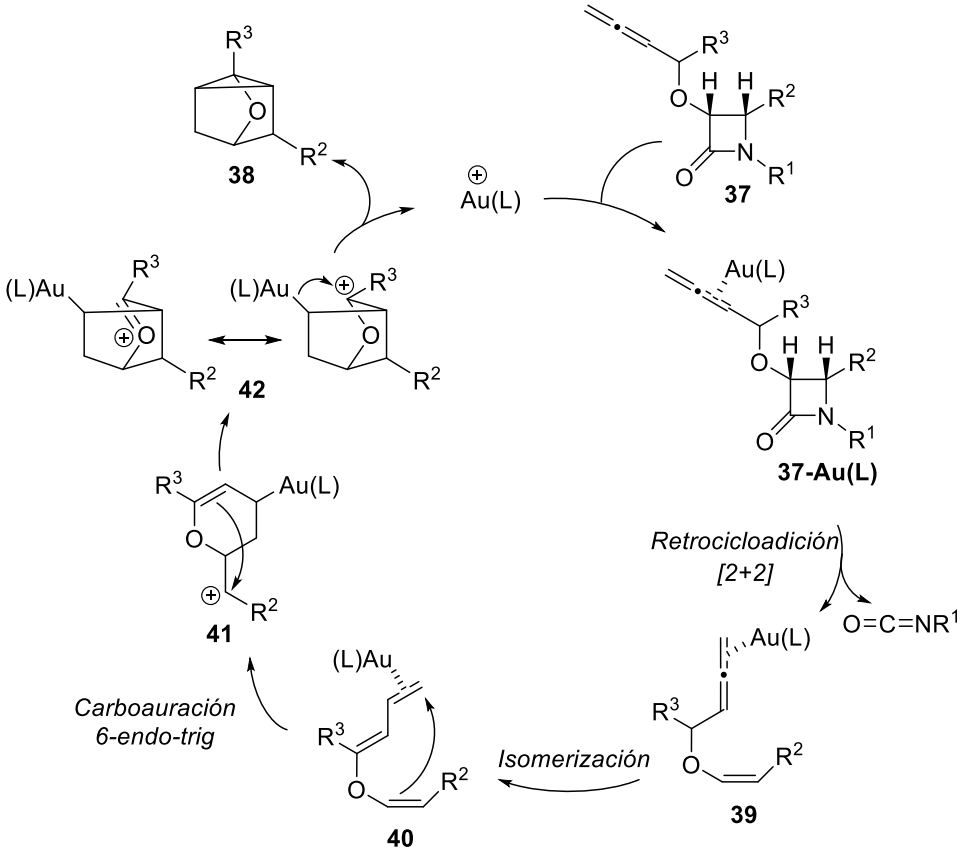
Esquema XI.20

La formación de los compuestos caja **38** a partir de las alenil-β-lactamas **37** se puede explicar a través del mecanismo de reacción propuesto en el Esquema XI.21 (apoyado en cálculos DFT). Éste implicaría una retrocicloadición [2+2] alqueno-isocianato poco común,[146] seguida de una isomerización alqueno-dieno que daría lugar a los enol éteres **40**,[147] los cuales sufrirían una carbociclación 6-*endo* quimio y regioselectiva, asociada con el ataque nucleófilo del carbono de la

146 La retrocicloadición [2+2] alqueno-isocianato puede ocurrir térmicamente, pero las energías de activación calculadas son altas: a) Rode, J. E.; Dobrowolski, J. C. *J. Phys. Chem. A* **2006**, *110*, 3723. b) Cossío, F. P.; Roa, G.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 12306. c) Paquette, L. A.; Wyvratt Jr., M. J.; Allen, G. R. *J. Am. Chem. Soc.* **1970**, *92*, 1763. Para el estudio mecanístico de la fragmentación β-lactámica catalizada por osmio, véase: d) Casarrubios, L.; Esteruelas, M.A.; Larramona, C.; Lledós, A.; Muntaner, J. G.; Oñate, E.; Ortuño, M. A.; Sierra, M. A. *Chem. Eur. J.* **2015**, *21*, 16781.

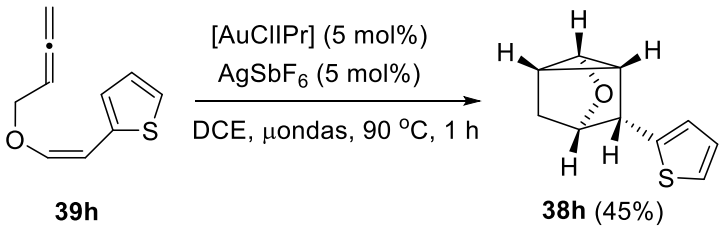
147 Para estudios sobre la isomerización aleno-dieno catalizada por oro véase: a) Chen, J.–M.; Chang, C.–J.; Ke, Y.–J.; Liu, R.–S. *J. Org. Chem.* **2014**, *79*, 4306. b) Basak, A.; Chakrabarty, K.; Ghosh, A.; Das, G. K. *J. Org. Chem.* **2013**, *78*, 9715. Para la iomerización de alquinos a 1,3-dienos, con alenos como intermedios, catalizada por oro, véase: Wang, Z.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc,* **2014**, *136*, 8887.

posición β del sustituyente heteroaromático (Esquema XI.21). Esta propuesta confirmaría los resultados experimentales obtenidos ya que sólo aquellos grupos ricos en electrones, que aumentarían la nucleofilia del átomo de carbono en β, son capaces de llevar a cabo la transformación estudiada.



Esquema XI.21

Por último, y con el fin de apoyar el mecanismo previamente explicado, decidimos sintetizar uno de los intermedios propuestos en el Esquema XI.21, el enol éter **39h**, y hacerlo reaccionar en las mismas condiciones de catálisis de oro. La reacción condujo al aducto **38h** con un rendimiento del 45%, confirmando así la presencia de este intermedio en el curso de la reacción (Esquema XI.22).



Esquema XI.22

Cabe mencionar en este punto que, aunque la economía atómica de la reacción es mayor partiendo de los alquenos **39**, que utilizando las alenil-β-lactamas **37**, la inestabilidad de estos enol-éteres junto con la dificultad de su preparación (nueve pasos de síntesis a partir del alcohol propargílico frente a los cuatro de las β-lactamas) confirman la mayor utilidad de las alenil β-lactamas como dienil-vinil éteres enmascarados. Asimismo, teniendo en cuenta que la preparación de los compuestos **39**, implica la liberación de un grupo TIP-, un sustituyente triflato y un ácido borónico, la economía atómica del proceso global juega a favor de los precursores derivados del anillo de 2-azetidinona.

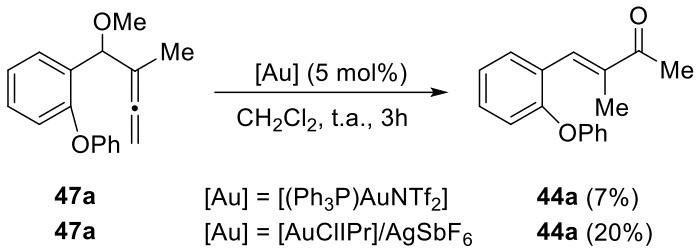
XI.2. Reacciones de transposición de alenos catalizadas por hierro

En la presente Memoria se describen dos metodologías diferentes de transposición de alenos catalizadas por hierro: una reacción de trasposición de tipo Meyer–Schuster y un reagrupamiento aza–Claisen unido a un proceso de fluoración.

XI.2.1. Capítulo 5: Síntesis de cetonas α,β-insaturadas disustituidas mediante un reagrupamiento tipo Meyer-Schuster en alenoles catalizado por ácido

En primer lugar, y una vez explorada la reactividad de ariloxialenos unidos a núcleos de importancia biológica como β-lactamas y azúcares (Capítulo 1) o el núcleo de indol (Capitulo 2), nos propusimos como nuevo objetivo el estudio de la reactividad de ariloxialenos unidos a un anillo aromático.

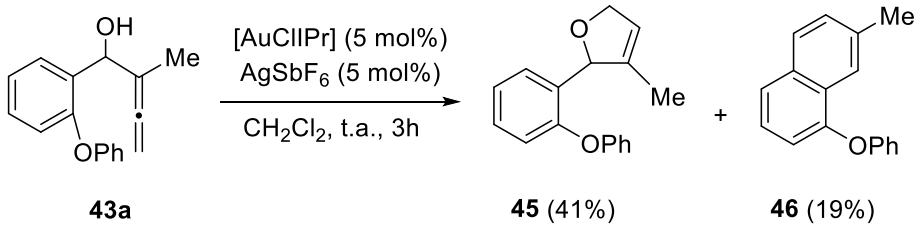
Para ello, se escogió como sustrato modelo el alenol **47a**, protegido como éter metílico para evitar reacciones de *O*-ciclación, y los catalizadores de oro previamente utilizados: el catalizador de Gagosz [$AuNTf_2(PPh_3)$] (Capítulos 1 y 2) y el sistema catalítico [AuIPrCl]/$AgSbF_6$ (Capítulos 3 y 4). Sorprendentemente, en ambos casos se obtuvo como único producto de reacción la cetona α,β-insaturada **44a**, en lugar del aducto de carbociclación cíclico esperado (Esquema XI.23).



Esquema XI.23

La formación de la enona **44a** puede explicarse a través de una reacción de transposición de Meyer-Schuster del α-alenol de partida **47a**. Debido a que en la literatura únicamente existen algunos ejemplos aislados de la citada transformación,[148] y que ésta puede representar una nueva ruta efectiva de síntesis de cetonas α,β-insaturadas sustituidas en la posición interna, decidimos estudiar su alcance y generalidad.

En primer lugar, exploramos la posibilidad de utilizar el α-alenol no protegido **43a**, que presentaba el grupo hidroxilo libre. Desafortunadamente, el tratamiento de este precursor con [AuIPrCl]/$AgSbF_6$ en diclorometano no dio lugar a la transposición de Meyer-Schuster deseada, obteniéndose una mezcla separable de los correspondientes aductos de oxiciclicación y carbociclación, **45** y **46** (Esquema XI.24).[149]

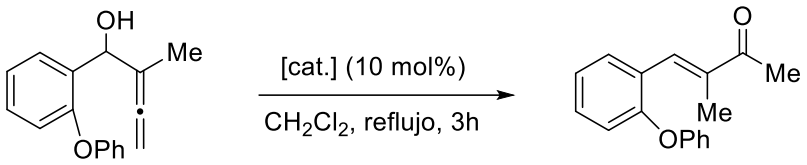


Esquema XI.24

148 Véase el apartado "II.1.2. Reacciones de transposición tipo Meyer-Schuster en alenos" en la sección "II. Antecedentes Generales".

149 Para ejemplos previos de este tipo de transformación véanse: a) Hashmi, A. S.K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1387. b) Asikainen, M.; Krause, N. *Adv. Synth. Catal.* **2009**, *351*, 2305; c) Kong, W.; Fu, C.; Ma, S. *Eur. J. Org. Chem.* **2010**, 6545.

A la vista de este resultado, y teniendo en cuenta la abundancia, el bajo coste y las buenas prestaciones medioambientales de los catalizadores de hierro,[150] decidimos estudiar si catalizadores tales como $FeCl_3 \cdot 6H_2O$ o $Fe(OTf)_3$ serían eficaces para llevar a cabo la reacción. Afortunadamente, el tratamiento del alenol **43a** con cualquiera de los dos catalizadores férricos en diclorometano a reflujo condujo a la cetona **44a** con rendimientos similares. Asimismo, el tratamiento con ácido tríflico condujo a la enona **44a** con un 65 % de rendimiento a baja temperatura (Esquema XI.25).

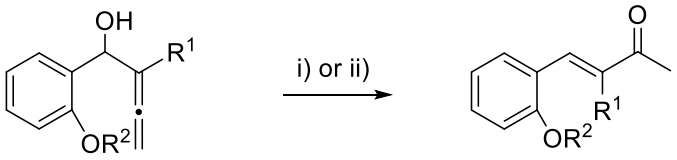


43a	[cat.] = $FeCl_3 \cdot 6H_2O$, reflujo, 3h	**44a** (52%)
43a	[cat.] = $Fe(OTf)_3$, reflujo, 14h	**44a** (47%)
43a	[cat.] = TfOH, -20 ºC, 14h	**44a** (65%)

Esquema XI.25

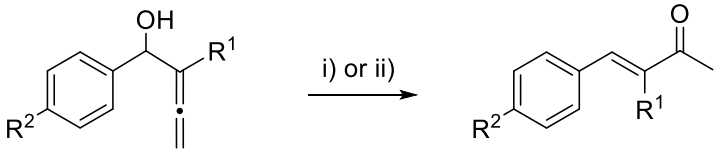
Una vez optimizadas las condiciones de reacción, decidimos estudiar el alcance de esta transposición en los α-alenoles **43b-k**, que presentaban tanto grupos metilo como grupos fenilo en el aleno, así como diferentes sustituyentes en el anillo aromático. Afortunadamente, el tratamiento de los alenoles metilsustituidos con ácido tríflico en diclorometano a -20 ºC condujo a las correspondientes cetonas α,β-insaturadas como únicos productos de reacción (Esquema XI.26). Por el contrario, los alenoles fenilsustituidos en las mismas condiciones de reacción dieron lugar a mezclas complejas, por lo que se decidió ensayar $Fe(OTf)_3$ en estos sustratos, obteniéndose las enonas correspondientes de manera satisfactoria (Esquema XI.26).

150 Para revisiones, véanse: a) Majumdar, K. C.; De, N.; Ghosh, T.; Roy, B. *Tetrahedron* **2014**, *70*, 4827. b) Klein, J. M. E. N.; Plietker, B. *Org. Biomol. Chem.* **2013**, *11*, 1271. c) Fürstner, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 1364. d) Bauer, E. B. *Curr. Org. Chem.* **2008**, *12*, 1341. e) *Iron Catalysis in Organic Chemistry*, Plietker, B, ed. Wiley-VCH, Weinheim, 2008; f) Correa, A.; García-Mancheño, O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. g) Fürstner, A.; Sherry, B. D. *Acc. Chem. Res.* **2008**, *41*, 1500. h) Díaz, D. D.; Miranda, P. O.; Padrón, J. I.; Martin, V. S. *Curr. Org. Chem.* **2006**, *10*, 457. i) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.



43b R^1 = Ph, R^2 = Ph
43c R^1 = Me, R^2 = 4-BrC_6H_4
43d R^1 = Me, R^2 = 2-PhC_6H_4

44b (51%, método ii)
44c (61%, método i)
44d (62%, método i)



43e R^1 = Me, R^2 = Cl
43f R^1 = Ph, R^2 = Cl
43g R^1 = Me, R^2 = MeO
43h R^1 = Ph, R^2 = MeO
43i R^1 = Me, R^2 = Me
43j R^1 = Ph, R^2 = Me
43k R^1 = Ph, R^2 = H

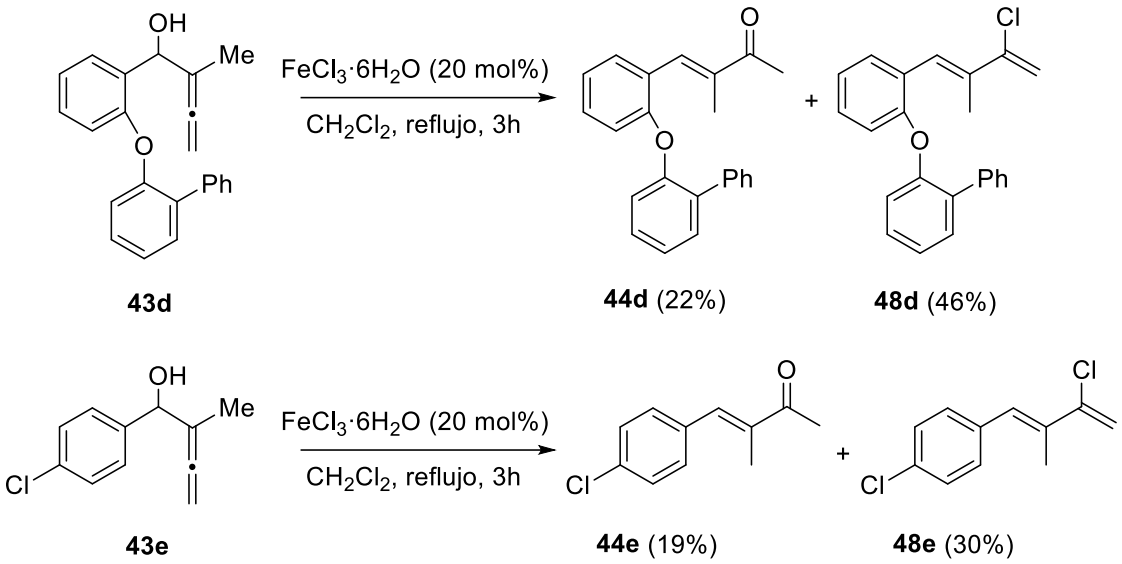
44e (70%, método i)
44f (55%, método ii)
44g (65%, método i)
44h (52%, método ii)
44i (61%, método i)
44j (51%, método ii)
44k (50%, método ii)

i) TfOH (10 mol%), CH_2Cl_2, -20 ºC, 14 h.
ii) $Fe(OTf)_3$ (10 mol%), CH_2Cl_2, reflujo, 14 h.

Esquema XI.26

Como se puede observar en el Esquema XI.26, la reacción es totalmente selectiva, obteniéndose únicamente los aductos procedentes de la trasposición de Meyer-Schuster, sin que aparezcan trazas de los productos de oxiciclación en ninguno de los casos. Además, tolera diferentes grupos funcionales, tanto electrodadores como electroaceptores, en el anillo aromático.

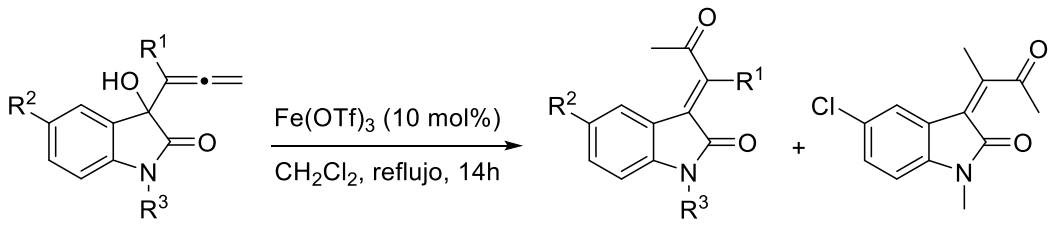
A la vista de este resultado, decidimos probar la eficacia del $FeCl_3 \cdot 6H_2O$ en dos de los alenoles previamente estudiados, los compuestos **43d** y **43e**. En ambos casos la reacción no fue selectiva, obteniéndose como productos mayoritarios los clorodienos **48d** y **48e** y como productos minoritarios los aductos Meyer-Schuster **44d** y **44e** (Esquema XI.27).



Esquema XI.27

Con el fin de extender esta nueva trasposición de Meyer-Schuster en α-alenoles derivados de grupos aromáticos diferentes del anillo de fenilo, y debido a la gran importancia del núcleo de indol y su análogo oxindol en Síntesis Orgánica (como ya se ha comentado en los Capítulos 2, 3 y 4), llevamos a cabo el tratamiento de los alenilindoles **49** y **52** con $Fe(OTf)_3$ en diclorometano a reflujo.

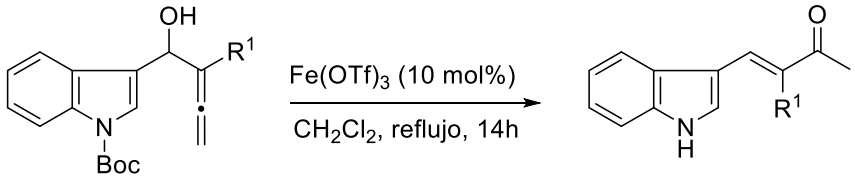
Los α-alenoles derivados de isatina **49** se transformaron de manera satisfactoria en las correspondientes enonas **50**, mostrando así la tolerancia de la reacción a diferentes sustituyentes en el núcleo de indol, tanto en el átomo de nitrógeno como en el anillo, así como en el sustituyente alénico (Esquema XI.28).



49a R^1 = Ph, R^2 = H, R^3 = Me — **50a** (57%)
49b R^1 = Ph, R^2 = H, R^3 = H — **50b** (64%)
49c R^1 = Ph, R^2 = Cl, R^3 = Me — **50c** (49%)
49d R^1 = Me, R^2 = Cl, R^3 = Me — **50d** (35%) — **51d** (12%)

Esquema XI.28

Asimismo, los 3-alenil-indoles *N*-Boc protegidos **52**, en las mismas condiciones de reacción, dieron lugar a las correspondientes cetonas desprotegidas **53** como únicos productos de reacción, pero con bajos rendimientos (Esquema XI.29)

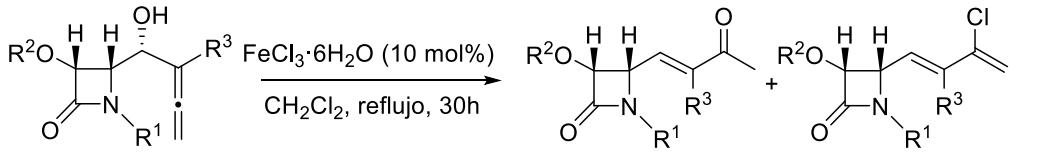


52a R^1 = Ph
52b R^1 = Me

53a (20%)
53b (24%)

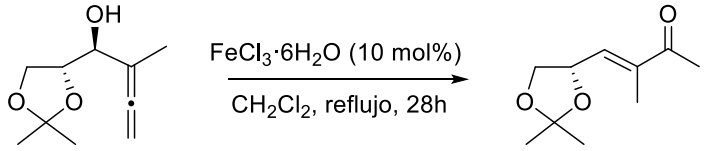
Esquema XI.29

Cuando se intentó extender la metodología estudiada a α-alenoles unidos a grupos alifáticos, por tratamiento de los sustratos enantiopuros **54-56** con $Fe(OTf)_3$ o ácido tríflico, no se obtuvieron los aductos Meyer-Schuster correspondientes. Sin embargo, la utilización de $FeCl_3 \cdot 6H_2O$ condujo a la formación las cetonas **57**, **59** y **60**, aunque con bajos rendimientos, debido a la aparición de productos secundarios (Esquema XI.30).



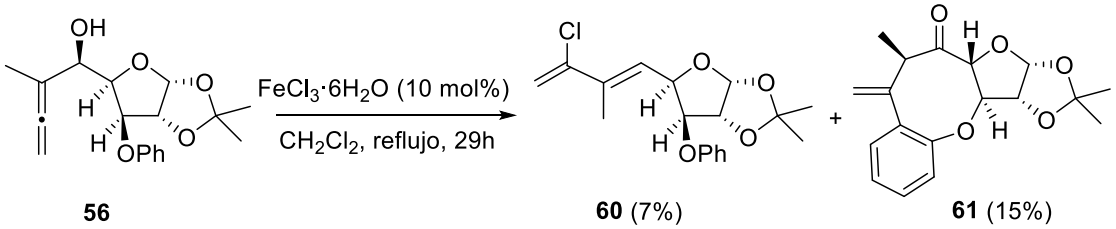
54a R^1 = isobutilo, R^2 = Ph, R^3 = Me
54b R^1 = isobutilo, R^2 = Ph, R^3 = Ph
54c R^1 = Bn, R^2 = Ph, R^3 = Me
54d R^1 = R^2 = 4-$MeOC_6H_4$, R^3 = Me

57a (8%) **58a** (9%)
(*E*)-**58b** (27%)/(*Z*)-**58b** (10%)
57c (20%)
57d (31%)



55

59 (24%)



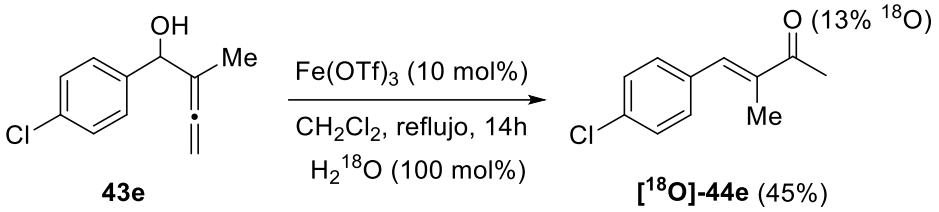
56

60 (7%)

61 (15%)

Esquema XI.30

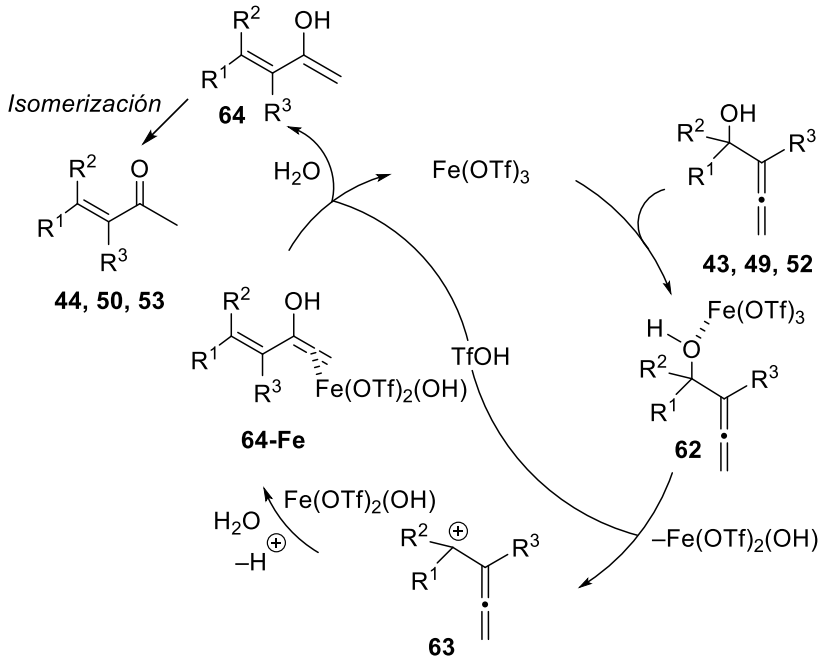
Por último, y con el fin de obtener más información sobre el mecanismo de esta reacción, decidimos llevar a cabo un experimento de marcaje isotópico con O^{18}. Así, el tratamiento del alenol **43a** con $Fe(OTf)_3$ en presencia de 100 mol% de H_2O^{18} condujo a la cetona α,β-insaturada, parcialmente marcada con O^{18}, **44e**; confirmando de esta forma que el oxígeno del grupo carbonilo procede del H_2O presente en el medio de reacción (Esquema XI.31).



43e **[^{18}O]-44e** (45%)

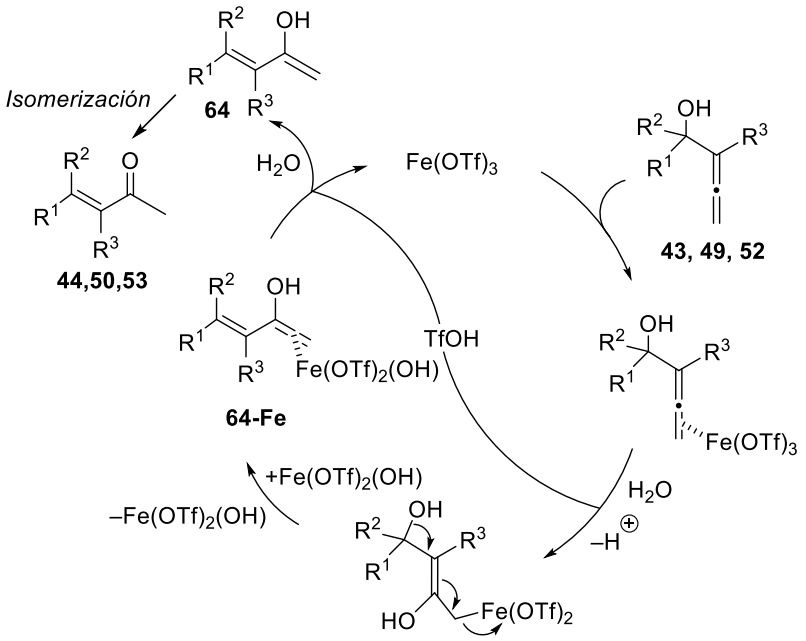
Esquema XI.31

Este resultado junto con la alta estereoselectividad de la reacción, obteniéndose de forma exclusiva en todos los casos los alquenos *Z* independientemente del α-alenol de partida (excepto en el sustrato **49d**, Esquema XI.28), puede indicar la presencia de especies carbocatiónicas en el mecanismo de la misma. Debido a ello, la formación de las cetonas α,β-insaturadas podría explicarse a través del camino de reacción, eliminación-adición, propuesto en el Esquema XI.32.



Esquema XI.32

Así, la formación de los productos procedentes de la transposición de Meyer-Schuster implicaría la liberación del grupo alcohol en primer lugar, generando un catión alénico, el cual sufriría posteriormente el ataque nucleófilo del agua del medio de reacción (Esquema XI.32). Sin embargo, el mecanismo de adición-eliminación alternativo tampoco puede ser completamente descartado (Esquema XI.33).



Esquema XI.33

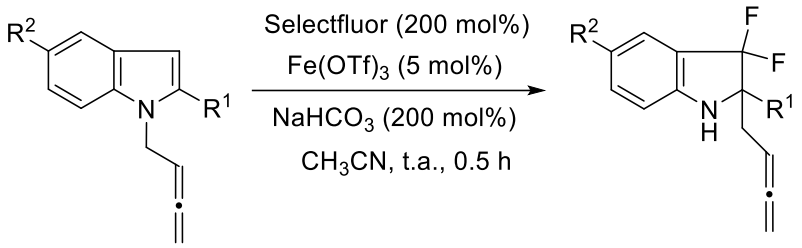
XI.2.2 Capítulo 6: Fluoración/Reagrupamiento alénico aza–Claisen en indoles catalizados por hierro

Debido a la importancia biológica de los compuestos fluorados[151] y una vez estudiada la interesante reactividad que presentan tanto los 2- como los 3-alenilindoles (Capítulo 2 y 5), decidimos llevar a cabo el estudio de la reacción de fluorofuncionalización de *N*-alenil-indoles por catálisis metálica.

Para ello, escogimos como materiales de partida los *N*-alenil-indoles **66** y Selectfluor como agente de fluoración electrófilo. Una vez optimizadas las condiciones de reacción, se observó que era necesaria la presencia conjunta de

151 Véanse referencias 9, 114 y 115.

una base, el $NaHCO_3$, y un ácido de Lewis, el $Fe(OTf)_3$, para que el proceso se completara. De esta forma, el tratamiento de los alenil-indoles **66a-k** en estas condiciones de reacción utilizando acetonitrilo como disolvente y a temperatura ambiente, condujo a las difluoroindolinas **67a-k** como únicos productos de reacción con rendimientos razonables (Esquema XI.34).



66a R^1 = Ph, R^2 = H	**67a** (83%)
66b R^1 = 4-ClC_6H_4, R^2 = H	**67b** (66%)
66c R^1 = 4-FC_6H_4, R^2 = H	**67c** (40%)
66d R^1 = 4-MeC_6H_4, R^2 = H	**67d** (48%)
66e R^1 = 4-*t*BuC_6H_4, R^2 = H	**67e** (43%)
66f R^1 = naftalen-2-il, R^2 = H	**67f** (55%)
66g R^1 = 4-MeC_6H_4, R^2 = Me	**67g** (52%)
66h R^1 = 4-MeC_6H_4, R^2 = OMe	**67h** (42%)
66i R^1 = 4-MeC_6H_4, R^2 = F	**67i** (44%)
66j R^1 = Ph, R^2 = NO_2	**67j** (92%)[a]
66k R^1 = Ph, R^2 = CN	**67k** (97%)[a]

[a]No fue necesaria la purificación cromatográfica.

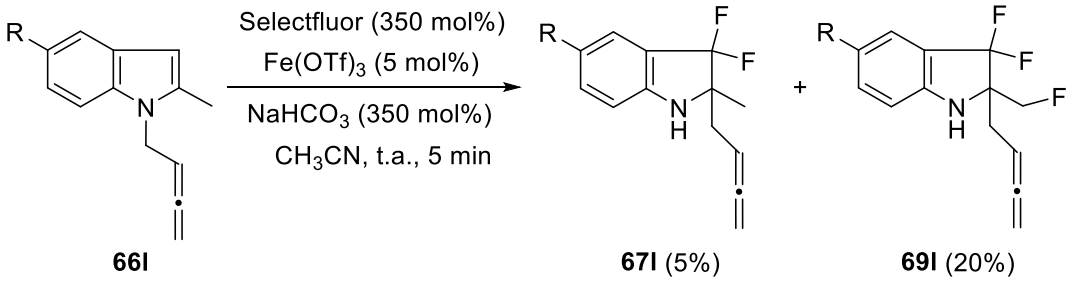
Esquema XI.34

Los compuestos **67**, además de incorporar dos átomos de flúor en su estructura, sufren un reagrupamiento alénico aza–Claisen N1-C2 en el núcleo de indol, no descrito previamente en la literatura.[152] Esta secuencia de fluoración seguida de reagrupamiento aza–Claisen tolera grupos funcionales de demanda electrónica variada en el anillo aromático de la posición C2, así como grupos voluminosos como el *terc*-butilfenilo o el naftilo.

152 Para una revisión del reagrupamiento Aza-Claisen, véase: a) Majumdar, K. C.; Bhattacharyya, T.; Chattopadhyay, B.; Sinha, B. *Synthesis,* **2009**, 2117. Para el reagrupamiento Claisen C2–C3 de indoles para formar alenil oxindoles, véase: b) Cao, T.; Linton, E. C.; Deitch, J.; Berritt, S.; Kozlowski, M. C. *J. Org. Chem.* **2012**, *77*, 11034. c) Cao, T.; Deitch, J.; E. C.; Deitch, J.; Kozlowski, M. C. *Angew. Chem. Int. Ed.* **2012**, *51*, 2448.

La sustitución en el núcleo indólico por grupos con distintos efectos electrónicos tampoco supone grandes cambios en la reactividad (Esquema XI.34).

A la vista de este resultado, y con el fin de estudiar el alcance de esta interesante reacción, decidimos llevar a cabo el tratamiento de los *N*-alenil-indoles **66l-q**, que presentaban un sustituyente metilo en lugar de un grupo aromático unido a la posición C2 del indol. El ensayo inicial con el sustrato **66l**, en las condiciones de reacción previamente optimizadas, condujo sorprendentemente a una mezcla separable de la difluroroindolina **67l** esperada y el compuesto **69l**, el cual incorpora un átomo adicional de flúor en el sustituyente metilo (Esquema XI.35).

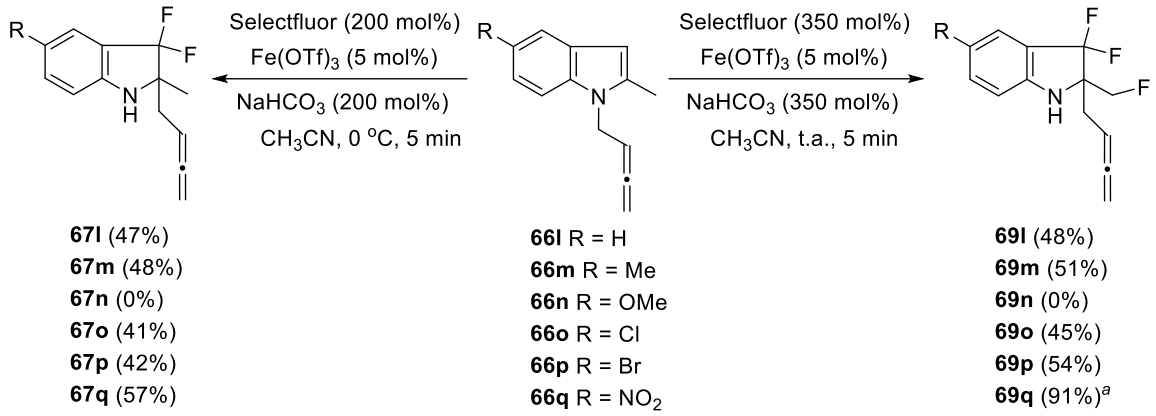


66l **67l** (5%) **69l** (20%)

Esquema XI.35

Debido al gran atractivo que representa la formación de un enlace C–F en un átomo de C_{sp3} mediante un reactivo de fluoración electrófilo,[153] decidimos optimizar unas nuevas condiciones de reacción con el fin de obtener tanto las difluoroindolinas **67** como las trifluoroindolinas **69** de forma totalmente selectiva. Finalmente, los compuestos difluorados **67** se obtuvieron como únicos productos de reacción cuando llevamos a cabo la reacción a baja temperatura, 0ºC, mientras que la obtención de los compuestos **69** requirió una cantidad superior de Selecftluor, 350 mol%, para que se produjera la incorporación de un átomo de flúor adicional en el sustituyente metílico (Esquema XI.36)

153 Para una revisión reciente, véase: Wu, J. *Tetrahedron Lett.* **2014***, **55**,* 4289.



67l (47%)
67m (48%)
67n (0%)
67o (41%)
67p (42%)
67q (57%)

66l R = H
66m R = Me
66n R = OMe
66o R = Cl
66p R = Br
66q R = NO_2

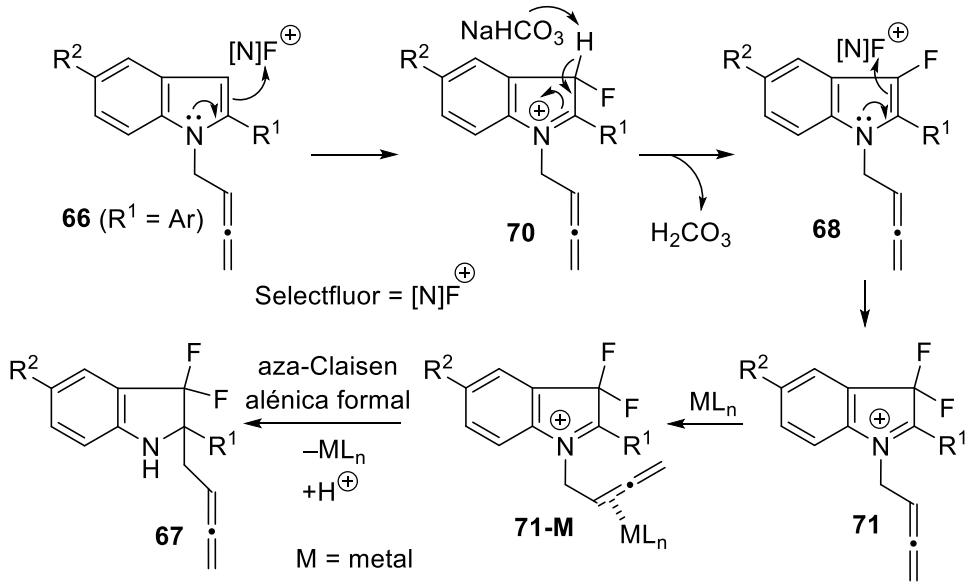
69l (48%)
69m (51%)
69n (0%)
69o (45%)
69p (54%)
69q (91%)[a]

[a]No fue necesaria la purificación cromatográfica

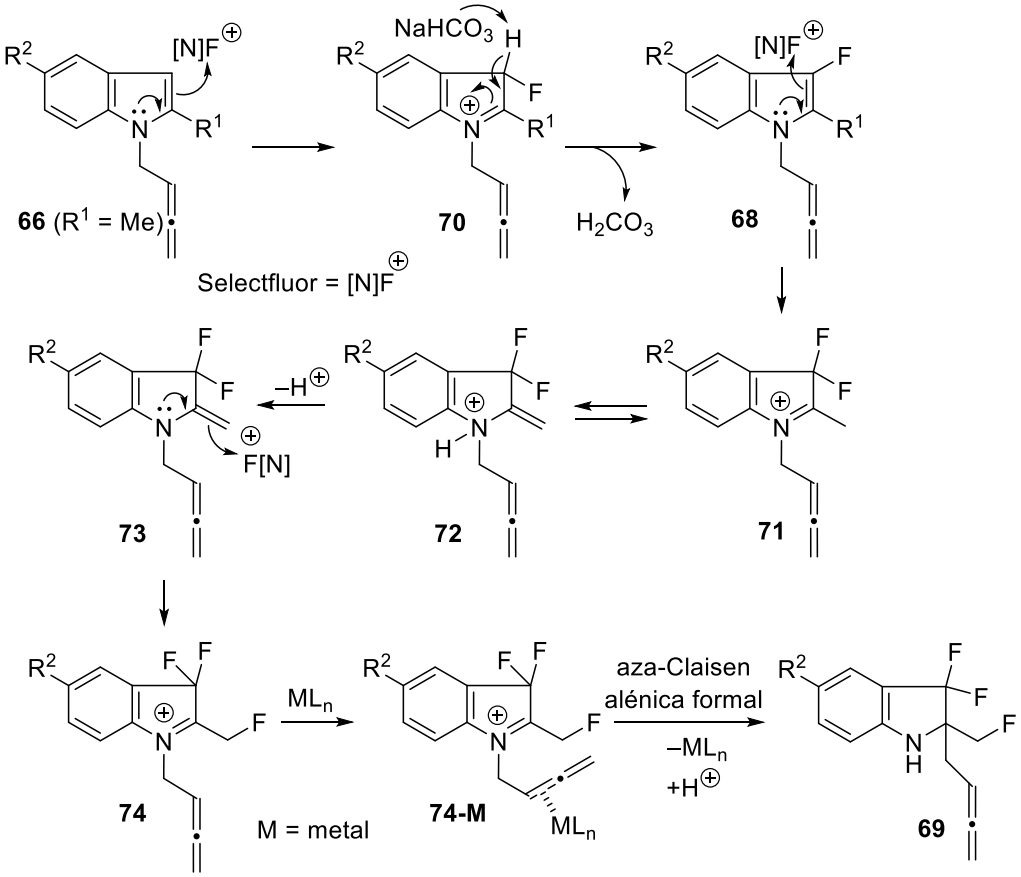
Esquema XI.36

Tanto la formación de las difluoroindolinas **67** como la de las trifluoroindolinas **69**, siguen un camino de reacción similar (Esquemas XI.37 y XI.38). En ambos casos, y tras una primera fluoración, la base desprotonaría la especie imínica formada dando lugar al alenil-indol monofluorado **68** y promoviendo el segundo ataque de la molécula de Selecftluor, como consecuencia de la estabilidad del catión imínico difluorado **71**. En este punto, la formación de los compuestos **67** implicaría un reagrupamiento formal aza–Claisen a través de la coordinación del catalizador metálico (Esquema XI.37), mientras que el proceso de formación de las trifluoroindolinas **69** requiere la formación de la enamina **73**, donde se produciría la tercera reacción de fluoración seguida del reagrupamiento aza–Clasien (Esquema XI.38).

Finalmente, con el fin de tener más información sobre el mecanismo propuesto, aislamos el alenil-indol monofluorado **68a** y llevamos a cabo su tratamiento en las mismas condiciones de reacción utilizadas para los alenil-indoles **66**. Este ensayo condujo a la formación de la difuoroindolina **67a**, lo que pone de manifiesto la presencia del intermedio **68** en el camino de reacción seguido por el proceso de fluoración/reagrupamiento alénico aza-Claisen estudiado.

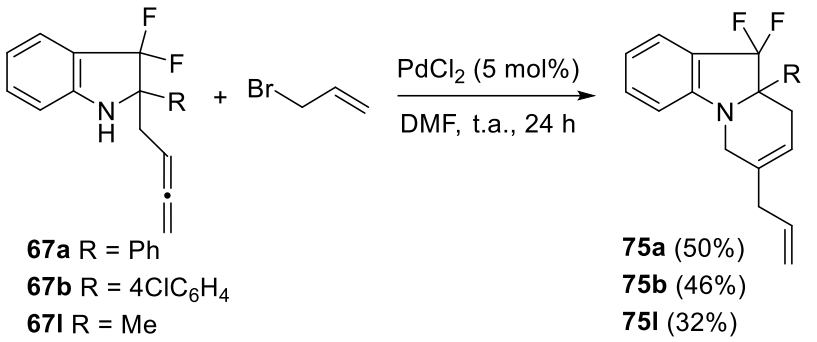


Esquema XI.37



Esquema XI.38

Por último, y debido a la importancia biológica que presentan las indolinas *N*-fusionadas,[154] decidimos llevar a cabo la reacción de carbociclación de las difluoroindolinas **67** previamente formadas, mediante el empleo de bromuro de alilo y catálisis de paladio en DMF. La reacción dio lugar a las indolinas *N*-fusionadas **75** como únicos productos de reacción (Esquema XI.39).



67a R = Ph
67b R = 4ClC$_6$H$_4$
67l R = Me

75a (50%)
75b (46%)
75l (32%)

Esquema XI.39

XI.3. Reacciones de [3]-cumulenoles catalizadas por metales de transición

Para finalizar el presente trabajo se ha llevado a cabo el estudio de diferentes reacciones de ciclación de 2,3,4-trien-1-oles diferentemente sustituidos catalizadas por sales de oro y paladio.

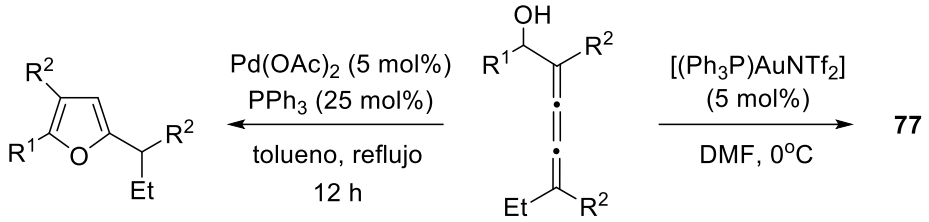
XI.3.1. Capítulo 7: Reacciones de ciclación de 2,3,4-trien-1-oles catalizadas por metales

Una vez explorada la reactividad de α-alenoles catalizada por metales de transición (Capítulo 1, 2 y 5), nos planteamos como nuevo objetivo el estudio de la

154 a) Hata, T.; Sano, Y.; Sugawara, R.; Matsumae, A.; Kanamori, K.; Shima, T.; Hoshi, T. *J. Antibiot. Ser. A* **1956**, *9*, 141. b) Bös, M.; Jenck, F.; Martin, J. R.; Moreau, J. L.; Mutel, V.; Sleight, A. J.; Widmer, U. *Eur. J. Med. Chem.* **1997**, *32*, 253. c) Goldbrunner, M., Loidl, G.; Polossek, T.; Mannschreck, A.; Angerer, E. V. *J. Med. Chem.* **1997**, *40*, 3524. d) Ames, B. D.; Liu, X.; Walsh, C. T. *Biochemistry* **2010**, *49*, 8564. e) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447. f) Cai, S.; Du, L.; Gerea, A. L.; King, J. B.; You, J.; Cichewicz, R. H. *Org. Lett.* **2013**, *15*, 4186. El núcleo tricíclico de hidropirido[1,2-*a*]-indol es precursor de diferentes alcaloides y productos bioactivos: g) Riofski, M. V.; John, J. P.; Zheng, M. M.; Kirshner, J.; Colby, D. A. *J. Org. Chem.* **2011**, *76*, 3676. h) England, D. B.; Padwa, A. *J. Org. Chem.* **2008**, *73*, 2792. i) Taylor, D. L.; Ahmed, P. S.; Chambers, P.; Tyms, A. S.; Bedard, J.; Duchaine, J.; Falardeau, G.; Lavallée, J. F.; Brown, W.; Rando, R. F.; Bowlin, T. *Antiviral Chem. Chemother.* **1999**, *10*, 79. j) Iino, T.; Katsura, M.; Kuriyama, K. *J. Pharmacol. Exp. Ther.* **1996**, *278*, 614. k) Kato, M.; Nishino, S.; Ito, K.; Takasugi, H. *Chem. Pharm. Bull.* **1995**, *43*, 1346.

reactividad de sus análogos superiores, los [3]-cumulenoles frente a catálisis metálica.

Para ello, escogimos como materiales de partida los 2,3,4-trien-1-oles **76a-e**, sintetizados por reacción de acoplamiento promovida por zirconio entre 1,3-butadiinos y aldehídos distintamente sustituidos,[155] y los hicimos reaccionar con distintos catalizadores de platino, oro y paladio. Los mejores resultados se obtuvieron para el catalizador de Gagosz [$AuNTf_2(PPh_3)$] en DMF a 0ºC y el catalizador de $Pd(OAc)_2$ en presencia de PPh_3 a reflujo de tolueno, obteniéndose en ambos casos los furanos trisustituidos **77a-e** como únicos productos de reacción con buenos rendimientos (Esquema XI.40).



77a (80%)	**76a** R^1 = Ph, R^2 = Ph	**77a** (81%, 12 h)
77b (86%)	**76b** R^1 = 2-furilo, R^2 = Ph	**77b** (90%, 5 h)
77c (61%)	**76c** R^1 = 2-tiofenilo, R^2 = Ph	**77c** (42%, 12 h)
77d (48%)	**76d** R^1 = Ph, R^2 = *n*-Pr	**77d** (37%, 12 h)
77e (76%, $R^2(-C_{sp3})$ = H)	**76e** R^1 = Ph, R^2 = $SiMe_3$	**77e** (79%, $R^2(-C_{sp3})$ = H, 14 h)

Esquema XI.40

El Esquema XI.40 muestra cómo la reacción transcurre de forma totalmente regioselectiva, a través de una oxiciclación 5-*endo*, sin observarse en ningún caso la formación de los posibles productos secundarios de deshidratación.[156]

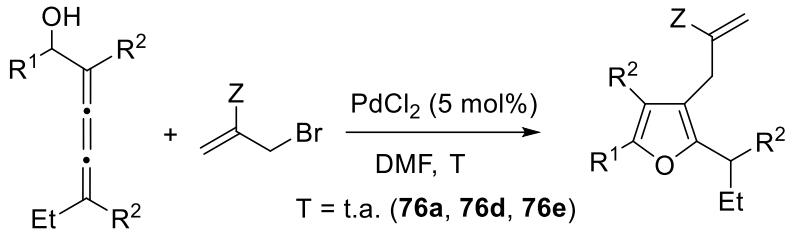
A la vista de este interesante resultado, decidimos estudiar el empleo de los [3]-cumulenoles **76**, como materiales de partida en reacciones de ciclación/funcionalización, utilizando las condiciones previamente optimizadas en nuestro grupo de investigación para los α-alenoles.[157] Así, el tratamiento de los sustratos **76a-e** con bromuro de alilo en presencia de $PdCl_2$ en DMF a temperatura ambiente condujo de forma exclusiva a los furanos tetrasustituidos **78aa-ec** por

155 Véase referencia 64a.

156 Para la preparación de dieninos π-conjugados por la reacción de deshidratación de [3]-cumulenoles catalizada por $TsOH·H_2O$, véase referencia 68b.

157 Véase referencia 19a.

reacción de oxiciclación seguida de una reacción de acoplamiento cruzado (Esquema XI.41).



76a R^1 = Ph, R^2 = Ph — **78aa** Z = H (58%)
76a R^1 = Ph, R^2 = Ph — **78ab** Z = Me (57%)
76a R^1 = Ph, R^2 = Ph — **78ac** Z = Br (56%)
76b R^1 = 2-Furil, R^2 = Ph — **78ba** Z = H (65%)
76b R^1 = 2-Furil, R^2 = Ph — **78bb** Z = Me (79%)
76b R^1 = 2-Furil, R^2 = Ph — **78bc** Z = Br (59%)
76c R^1 = 2-Tiofenil, R^2 = Ph — **78ca** Z = H (66%)
76c R^1 = 2-Tiofenil, R^2 = Ph — **78cb** Z = Me (67%)
76c R^1 = 2-Tiofenil, R^2 = Ph — **78cc** Z = Br (61%)
76d R^1 = Ph, R^2 = *n*-Pr — **78da** Z = H (40%)
76d R^1 = Ph, R^2 = *n*-Pr — **78db** Z = Me (44%)
76d R^1 = Ph, R^2 = *n*-Pr — **78dc** Z = Br (30%)
76e R^1 = Ph, R^2 = $SiMe_3$ — **78ea** Z = H (76%, R^2(-C_{sp3}) = H)
76e R^1 = Ph, R^2 = $SiMe_3$ — **78eb** Z = Me (74%, R^2(-C_{sp3}) = H)
76e R^1 = Ph, R^2 = $SiMe_3$ — **78ec** Z = Br (46%, R^2(-C_{sp3}) = H)

Esquema XI.41

La secuencia de heterociclación/acoplamiento, al igual que la reacción de cicloisomerización anterior, tolera tanto grupos arilo como grupos alquilo en los [3]-cumulenoles de partida. Asimismo, en ambos casos, se produce la pérdida del grupo trimetilsililo unido al sustituyente alifático de los furanos **77e** y **78ea-ec**, procedentes de la ciclación del cumuleno TMS-disustituido **76e**.

La formación de los furanos **77** y **78** se puede explicar a través de un camino de reacción similar (Figura XI.3). El proceso (apoyado en cálculos DFT) comenzaría para ambos compuestos con una oxiciclación regioselectiva 5-*endo*-*dig*, seguido de la protonólisis del enlace C-Pd y posterior isomerización, para los furanos trisustituidos **77**, y de la coordinación del doble enlace C=C al fragmento metálico, dando lugar a la reacción de inserción, para los furanos tetrasustituidos

78. En este caso, la última etapa consistiría en una β-eliminación de bromuro seguida de la isomerización final (Figura XI.3).

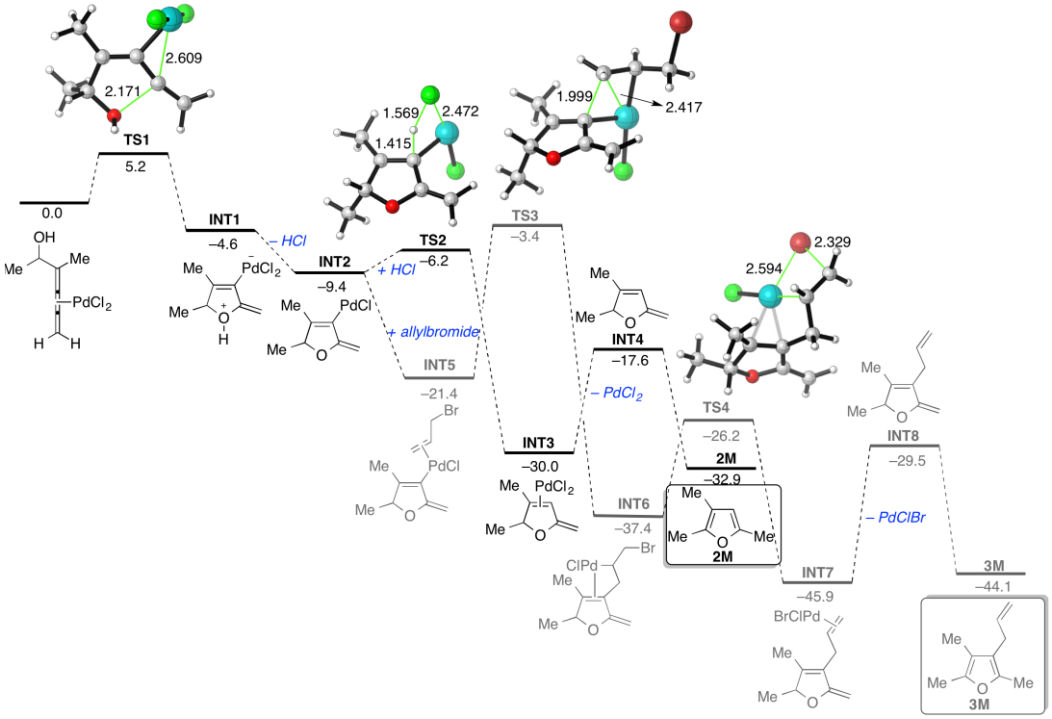
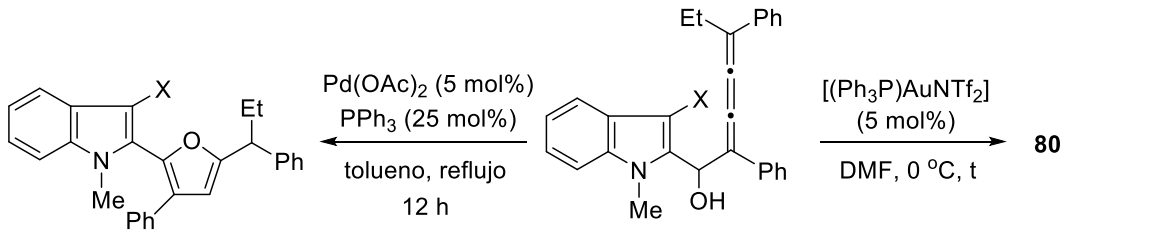


Figura XI.3

Continuando con nuestro interés en la reactividad de núcleos con potencial actividad biológica (Capítulos 2, 3, 4, 5 y 6), nos planteamos como siguiente objetivo la síntesis de [3]-cumulenoles unidos al núcleo indólico, no descritos previamente en la literatura, así como el estudio de su potencial sintético. El tratamiento de los 2,3,4-trien-1-oles derivados del anillo de indol **79** con catalizadores de oro y paladio en las condiciones previamente optimizadas, condujo a los furanos trisustituidos **80** como únicos productos de reacción (Esquema XI.42).



80a X = H (62%)
80b X = I (50%)

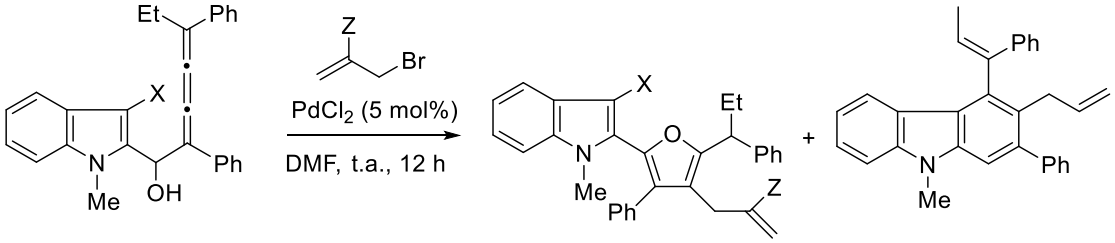
79a X = H
79b X = I

80a X = H (71%, 1h)
80b X = I (56%, 14h)

Esquema XI.42

Cabe mencionar que los cumulenos **79** pueden sufrir dos reacciones de ciclación diferentes, oxiciclación o carbociclación, debido a la presencia de dos centros nucleófilos en su estructura, el grupo hidroxilo y la posición C3 del anillo indólico. El Esquema XI.42 muestra cómo la reacción es totalmente quimio y regioselectiva dando lugar a los furanos **80** a través de una oxiciclación 5–*endo*, observándose un comportamiento similar al de los cumulenoles **76** previamente estudiados. [158]

La reacción de oxiciclación seguida de acoplamiento cruzado también condujo a los mismos resultados que los cumulenos simples, obteniéndose los furanos tetrasustiuidos **81** con rendimientos razonables. La reacción demostró ser quimioselectiva en todos los casos excepto en el sustrato **79a**, donde se observó la formación del carbazol **82aa** como producto minoritario (Esquema XI.43).



79a X = H
79a X = H
79a X = H
79b X = I
79b X = I
79b X = I

81aa Z = H (35%)
81ab Z = Me (44%)
81ac Z = Br (46%)
81ba Z = H (42%)
81bb Z = Me (61%)
81bc Z = Br (43%)

82aa (8%)

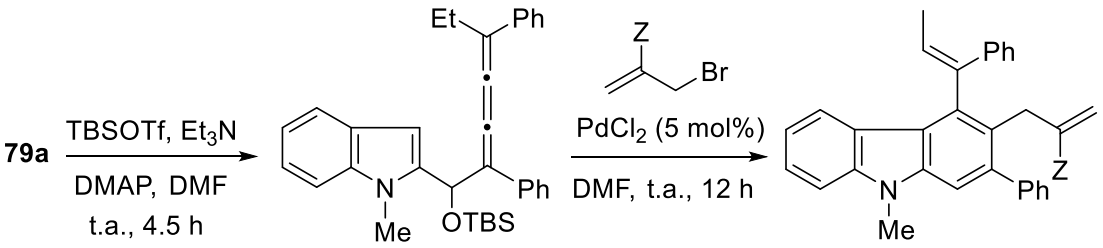
Esquema XI.43

Debido a la importancia del núcleo de carbazol, tanto por sus propiedades biológicas como por sus aplicaciones en ciencia de los materiales, [159] decidimos

158 La reactividad de los 2,3,4-trien-1-oles derivados de indol es contraria a la observada en los 2-alenil indoles, donde se produce de forma exclusiva la carbociclación 6-*endo*, véase: a) Capítulo 2, b) Referencias 24 y 25.

159 Para revisiones recientes, véanse: a) Referencia 139. b) Li, J.; Grimsdale, A. G. *Chem. Soc. Rev.* **2010**, *39*, 2399; d) Knölker*, H.–J. Chem. Lett.* **2009***, **38***, 13; e) Choi*, T. A.;* Czerwonka*,* R.; Forke*, R.;* Jäger*, A.;* Knöll*, J.;* Krahl*, M. P.;* Krause*, T.;* Reddy*, K. R.;* Franzblau, *S. J.;* Knölker*, H.–J. Med. Chem. Res.* **2008***, **17***,* 374; f) Knölker, *H.–J.;*Reddy*, K. R. Chemistry and Biology of Carbazole Alkaloids, in The Alkaloids,* vol. 65*, pp* 1–430, (Ed.: G. A. Cordell), *Academic Press,* Amsterdam, 2008; g) Knölker*, H.–J. Top. Curr. Chem.* **2005**, *244*, 115; h) Knölker, *H.–J.;* Reddy*, K. R. Chem. Rev.* **2002***, **102***,* 4303. Para ejemplos de materiales funcionales orgánicos basados en indoles: h) Wakim, S.; Bouchard, J.; Simard, M.; Drolet, N.; Tao, Y.; Leclerc, M.

llevar a cabo la reacción de carbociclación de los [3]-cumulenoles **79**. Para ello, y con el fin de evitar la reacción de oxiciclación, protegimos el grupo hidroxilo en forma de OTBS. De esta forma, el tratamiento del 2,3,4-trien-1-ol protegido con el grupo sililo **83** en presencia de $PdCl_2$ con bromuro de alilo condujo a la formación de los carbazoles **82** por reacción de hidroarilación 6-*endo* (Esquema XI.44).



83 (76%)

82aa Z = H (38%)
82ab Z = Me (31%)

Esquema XI.44

Finalmente, y con el fin de obtener más información acerca del mecanismo del proceso, estudiamos la reactividad de los [3]-cumulenoles derivados del núcleo de indol **79** a través de cálculos DFT. Como se puede observar en la Figura XI.4, la reacción de oxiciclación presenta una barrera de energía menor que la correspondiente a la de carbociclación, lo que explicaría la quimioselectividad observada en los resultados obtenidos de forma experimental.

Asimismo, este hecho justifica la necesidad de bloquear el grupo hidroxilo para llevar a cabo la síntesis de los carbazoles **82**, formados a través de una reacción de carbociclación 6-*endo* quimio y regioselectiva seguida de un acoplamiento cruzado, según muestra el mecanismo propuesto en el Esquema XI.45.

Chem. Mater. **2004**, *16*, 4386; i) Boudreault, P. L. T.; Wakim, S.; Blouin, N.; Simard, M.; Tessier, C.; Tao, Y.; Leclerc, M. *J. Am. Chem. Soc.* **2007**, *129*, 9125; j) Blouin, N.; Leclerc, M. *Acc. Chem. Res.* **2008**, *41*, 1110; k) Li, K.; Grimsdale, A. C. *Chem. Soc. Rev.* **2010**, *39*, 2399; l) Mansaray, H. B.; Kelly, M.; Vidovic, D.; Aldridge, S. *Chem. Eur. J.* **2011**, *16*, 5381; m) Nie, H.; Zhao, Y.; Zhang, M.; Ma, Y.; Baumgarten, M.; Müllen*, K. Chem. Commun.* **2011***, **47**,* 1234. n) Kim, S. M.; Byeon, S. Y.; Hwang, S.–H.; Lee, J. Y. *Chem. Commun.* **2015***, **51**,* 10672. o) Pho, T. V.; Yuen, J. D.; Kurzman, J. A.; Smith, B. G.; Miao, M.; Walker, W. T.; Seshadri, R.; Wudl, F. *J. Am. Chem. Soc.* **2012**, *134*, 18185.

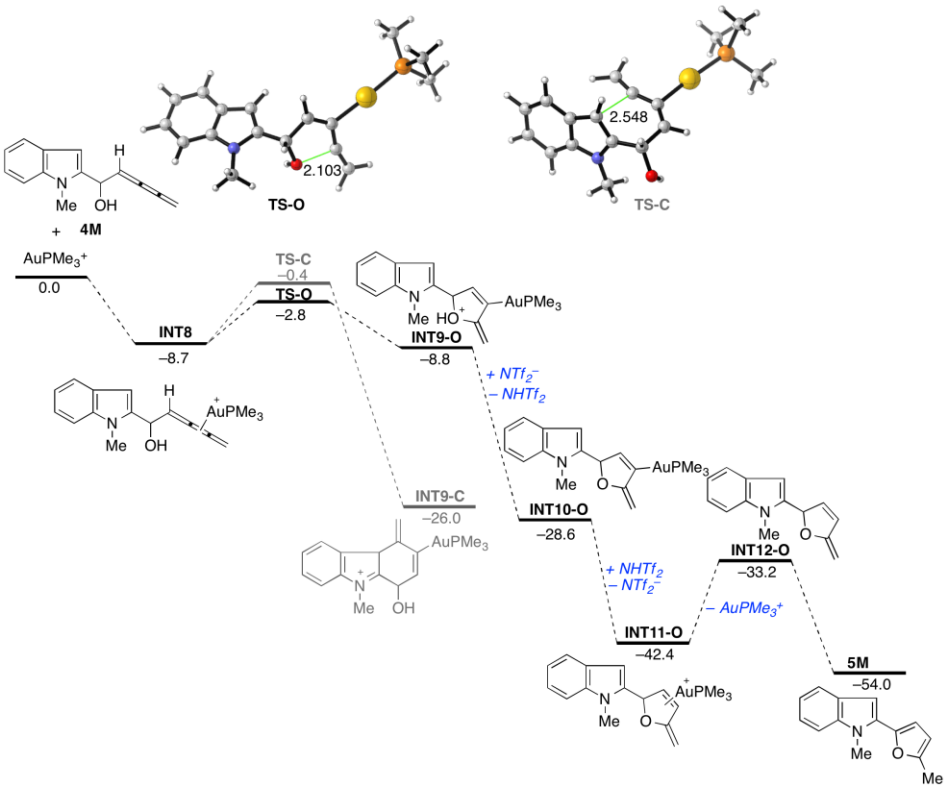
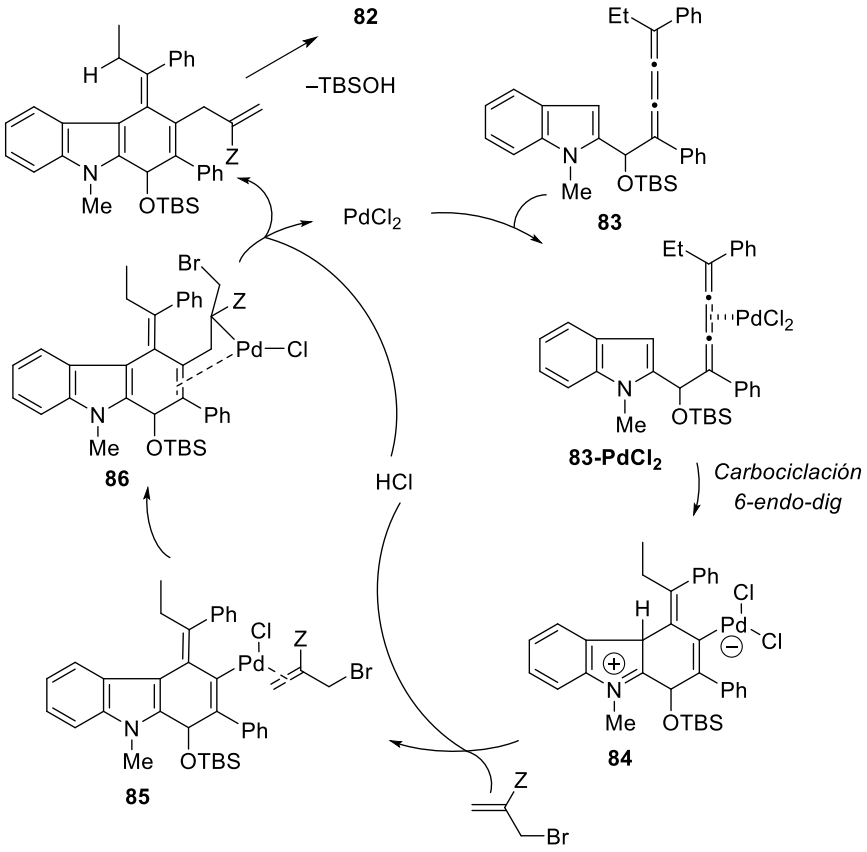


Figura XI.4



Esquema XI.45

XII. CONCLUSIONES

XII. CONCLUSIONES

El trabajo de investigación recogido en la presente Memoria ha pretendido contribuir al desarrollo de nuevas metodologías de ciclación y transposición de alenos y cumulenos catalizadas por metales para la preparación de sistemas policíclicos estructuralmente novedosos, así como moléculas con potencial actividad biológica. Las principales conclusiones de este estudio se resumen a continuación:

1. Se ha investigado la reacción de carbociclación catalizada por oro de diferentes alenos unidos a núcleos de importancia biológica, como son el anillo β-lactámico y el azúcar glucofuranosa. Mientras que las alenil-β-lactamas sufren una hidroarilación 9-*endo* para dar lugar a benzociclos fusionados de nueve miembros, los alenilazúcares conducen a ciclopentenos bicíclicos a través de una hidroalquilación 5-*exo* poco común.

2. Se ha estudiado la reactividad de alenil-indoles diferentemente sustituidos en la posición C3 del anillo indólico. Tanto por catálisis de oro como de paladio, distintos 3-yodoalenil-indoles se transformaron en yodocarbazoles, a través de una novedosa reacción de migración-1,3 de yodo. Por el contrario, los 3-fenoxialenil indoles condujeron a 1-oxicarbazoles mediante catálisis de oro a través de una carbociclación 6-*endo* con eliminación de fenol.

3. Partiendo de alenil-indoles unidos a β-lactamas y a través de reacciones de carbociclación catalizadas por oro se ha desarrollado la preparación de una gran diversidad de compuestos tri- y tetracíclicos. La regioselectividad del proceso cambia dependiendo de la posición del anillo β-lactámico a la que se encuentra unido el sustituyente alénico y de la longitud de la cadena carbonada que le separe de éste.

4. Se ha descrito una inesperada síntesis diastereoselectiva de compuestos tensionados “tipo caja” a partir de alenil-β-lactamas diferentemente sustituidas utilizando catálisis de oro. El proceso implica la ruptura simultánea de los enlaces N1–C4 y C2–C3 del anillo β-lactámico y la formación simultánea de varios enlaces carbono–carbono.

5. Se ha desarrollado una metodología sencilla y directa de preparación de cetonas α,β-insaturadas a partir de α-alenoles mediante un reagrupamiento tipo

Meyer-Schuster utilizando un medio catalítico sostenible como son las sales de hierro o los protones.

6. Se ha estudiado la reacción de fluoración de *N*-alenil-indoles describiéndose un proceso dominó de fluoración/reagrupamiento alénico aza–Claisen catalizado por hierro para dar lugar a di- y trifluoroindolinas de forma totalmente selectiva.

7. Se ha llevado a cabo el estudio de la reactividad de 2,3,4-trien-1-oles mediante catálisis de oro y paladio. El proceso es quimio y regioselectivo obteniéndose furanos tri- y tetrasustituidos por reacción de oxiciclación. La protección del grupo hidroxilo en los [3]-cumulenoles derivados de indol permite que tenga lugar la reacción de carbociclación para formar carbazoles distintamente sustituidos.

XIII. RESÚMENES

XIII. RESÚMENES

XIII.1. Summary

XIII.1.1. Introduction

During the last 20 years the chemistry of allenes has been extensively studied due to their interesting reactivity. Allenes and cumulenes have metamorphosed from a laboratory curiosity to a versatile and uniquely reactive functional groups, allowing chemists to prepare a variety of compounds of chemical and biological interest.

Among the abroad range of reactions of this kind of compounds, intramolecular cyclization of allenes and cumulenes bearing a nucleophilic substituent are of particular interest. The appearance of regioselectivity problems in these cyclization processes has led to the development of a wide spectrum of metal- catalyzed methodologies that aim to control this issue.

On the other hand, among heterocycles, β-lactam and indole derivatives attracted greater attention due to their biological and pharmacological activities such as antibacterial, enzyme inhibitors, neurotransmitters and antitumorals.

Finally, fluoroorganic molecules feature peculiar biological activities because of their improved lipophilicity and metabolic stability. Besides, the dearomatization of indoles has received considerable attention in organic synthesis because of the bioactivity of the resulting indolines. In the last years, considerable efforts have been devoted to the fluorination of functionalised indoles because this methodology is a direct entry to diverse fluorinated indoline structures.

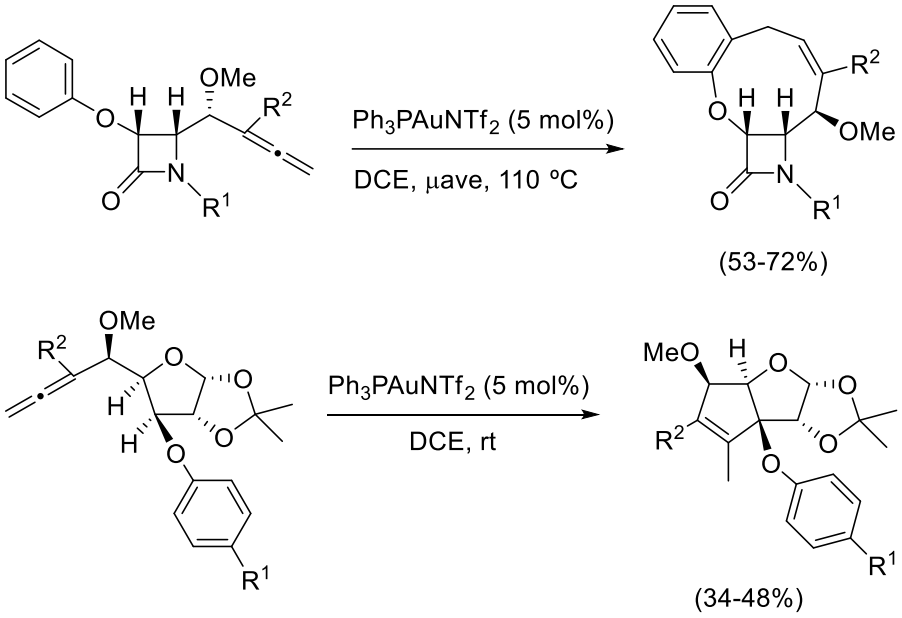
XIII.1.2. Objectives

The aim of this PhD Thesis is to develop new methodologies for the metal catalyzed cyclization and transposition of different allenes and higher [3]-cumulenes in order to synthesize novel complex structures. In particular, we have focused our attention in three different aspects: i) the development of novel carbocyclization reactions of allenes linked to biologically important cores, namely, β-lactam,

glucofuranose and indole; ii) the development of transposition reactions of allenes, iii) the study of the reactivity of [3]-cumulenols under metal catalysis.

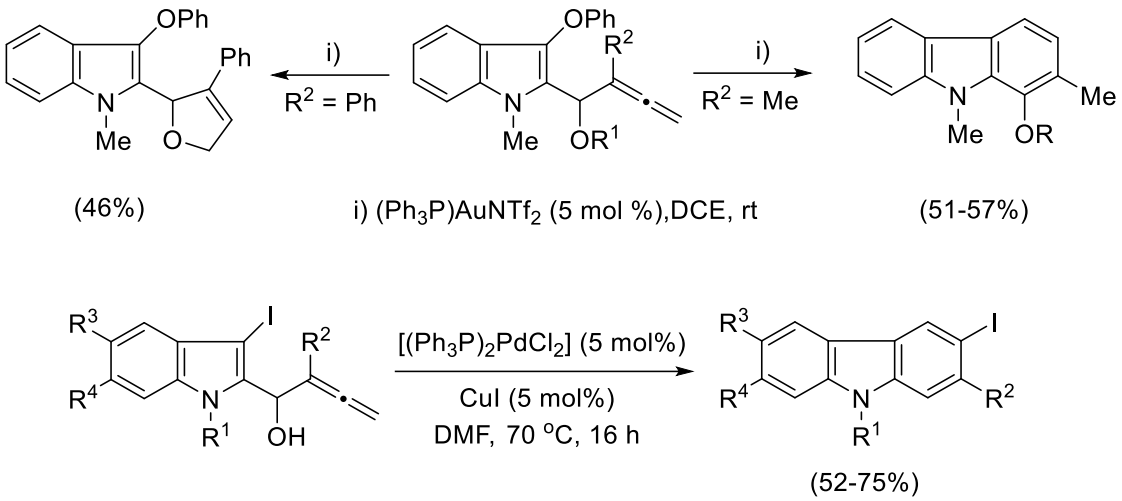
XIII.1.3. Results

First of all, a gold-catalyzed 9-*endo* carbocyclization of aryl allenes has been developed as a powerful synthetic tool to obtain novel nine-membered annulated β-lactam derivatives. In contrast, allenyl sugars provides fused cyclopentenes from a rare 5-*exo* hydroalkylation. Thus, it was shown that the outcome of the reaction can be modulated by the allene tether (Scheme XIII.1)



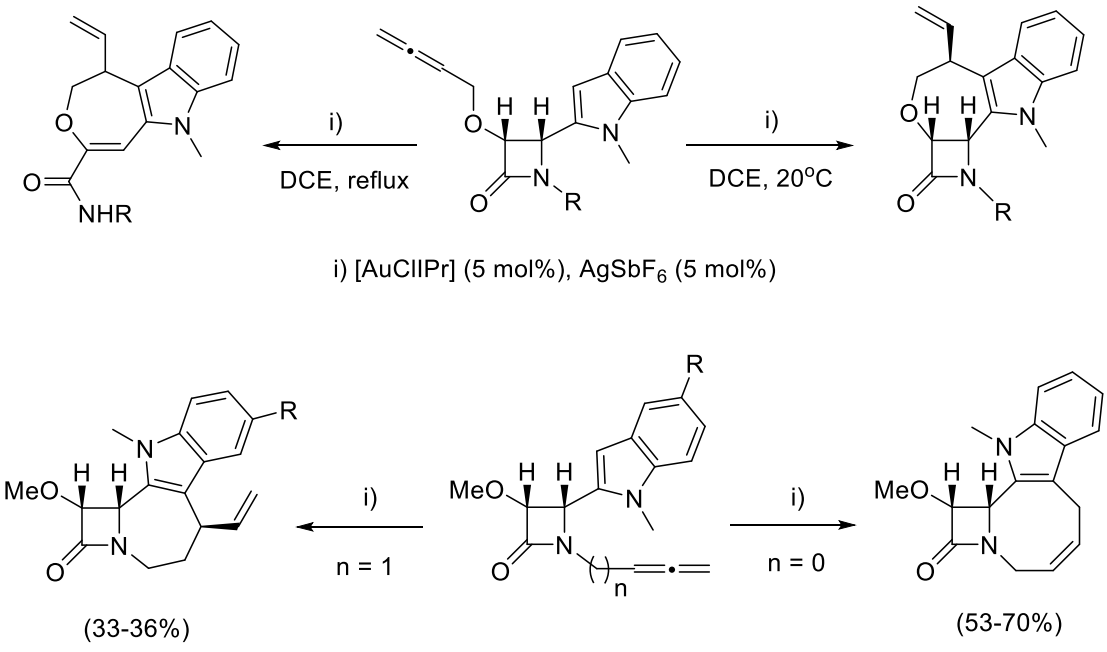
Scheme XIII.1

Taking advantage of indole-tethered allenes, an unprecedented intramolecular 1,3-iodine migration was described. In salient contrast to the gold or palladium catalysed reaction of 3-phenoxy-(indol-2-yl)allenes, which were transformed into 1-oxygenated carbazoles, 3-iodo-(indol-2-yl)allenes afforded 3-iodocarbazoles through rare recycling of halogen groups via 1,3-halogen migration (Scheme XIII.2).



Scheme XIII.2

On the other hand, gold-catalyzed hydroarylation reaction of β-lactam-tethered allenyl indoles gives a wide variety of policylic compounds with very high levels of stereo- and regioselectivity. Besides, a novel gold-catalyzed domino process, namely, the allenic hydroarylation/N1−C4 β-lactam bond breakage has been discovered (Scheme XIII.3)

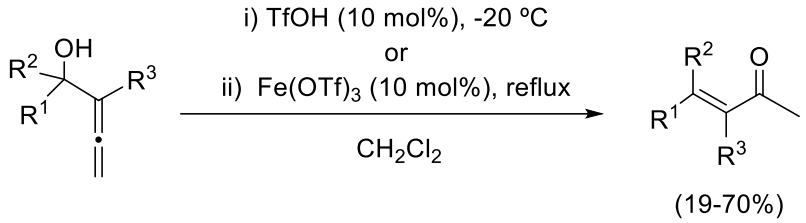


Scheme XIII.3

Moreover, it has been developed a diastereoselective synthesis of strained adducts which show cage-like structure directly from 3-allenyl-4-aryl(alkenyl)β-lactams through a novel an unanticipated reactivity in gold catalysis (Scheme XIII.4).

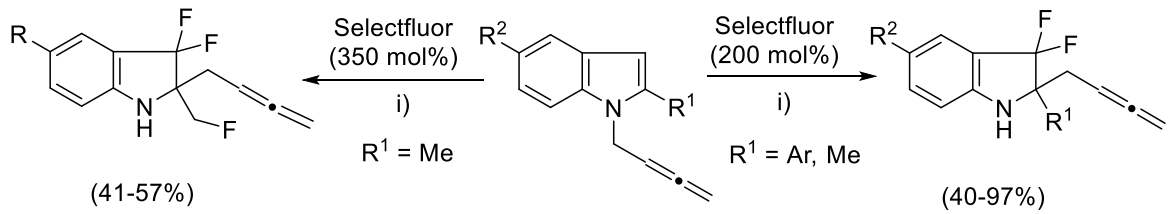
Scheme XIII.4

Considering the inexpensiveness and environmentally friendliness of iron catalysis, it has been developed a novel, direct and simple iron-catalyzed methodology to gain access to α,β-disubstituted conjugated enones by a Meyer-Schuster type rearrangement in α-allenols (Scheme XIII.5).



Scheme XIII.5

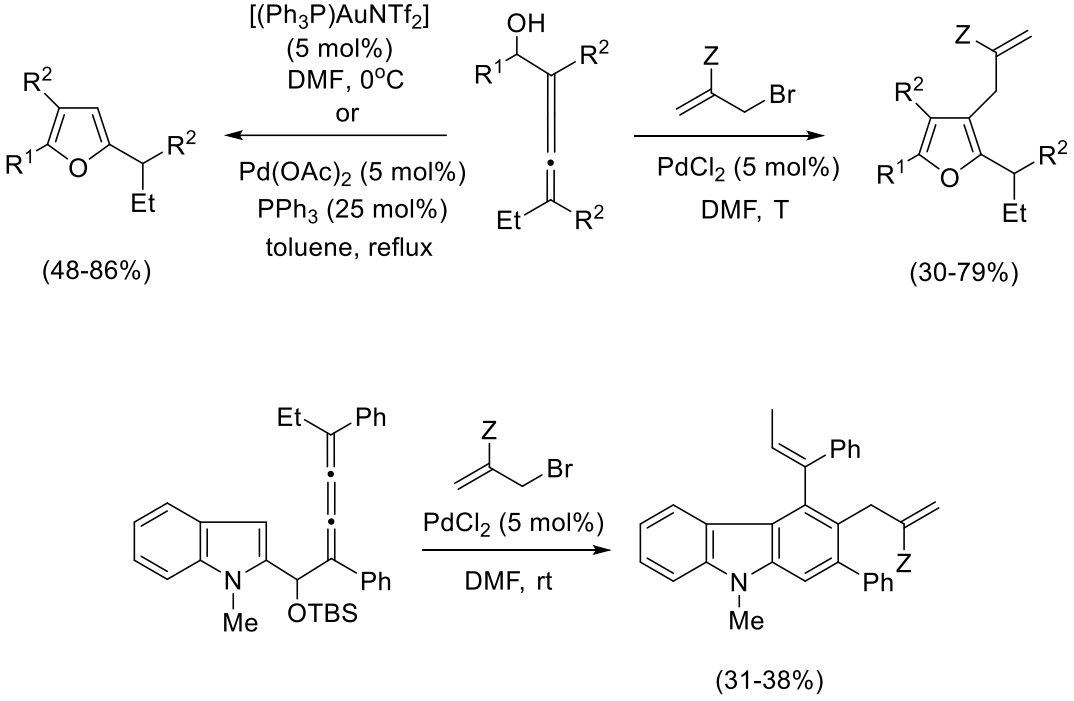
In addition, due the important properties of both polyfluorinated molecules as well as fused indolines, it has been accomplished the synthesis of di- and trifluoroindolines, taking advantage of the reaction between *N*-allenyl-indoles and Selectfluor under sustainable iron catalysis (Scheme XIII.6).



i) $Fe(OTf)_3$ (5 mol%), $NaHCO_3$ (200 mol%), CH_3CN, rt o 0 ºC

Scheme XIII.6

Finally, it has been started the study of higher cumulenes reactivity. In this research, the controlled preparation of tri- and tetrasubstituted furans, as well as carbazoles has been achieved through chemo- and regioselective metal-catalyzed cyclization reactions of cumulenic alcohols (Scheme XIII.7).



Scheme XIII.7

XIII.1.4. Conclusions

Several cyclization and/or functionalization reactions of allenyl substrates catalyzed by transition-metal salts have been developed, especially in the context of the synthesis of compounds with novel structures with potential biological interest. These methodologies are remarkable examples of the rapid construction of novel heterocyclic scaffolds using simple, chemo-, stereo and regioselective processes.

XIII.2. Resumen

XIII.2.1. Introducción

En los últimos 20 años, los alenos y cumulenos se han convertido en grupos funcionales versátiles con una reactividad única, permitiendo acceder a una gran variedad de compuestos de alto interés químico y biológico.

En especial, las reacciones de ciclación de alenos con un sustituyente nucleófilo catalizadas por metales de transición han experimentado un notable desarrollo en los últimos años.

Por otro lado, los compuestos heterocíclicos que contienen un núcleo β-lactámico y/o indólico en su estructura son particularmente relevantes debido a su presencia en productos naturales y sintéticos con actividad biológica, tales como antibióticos, aminoácidos u hormonas.

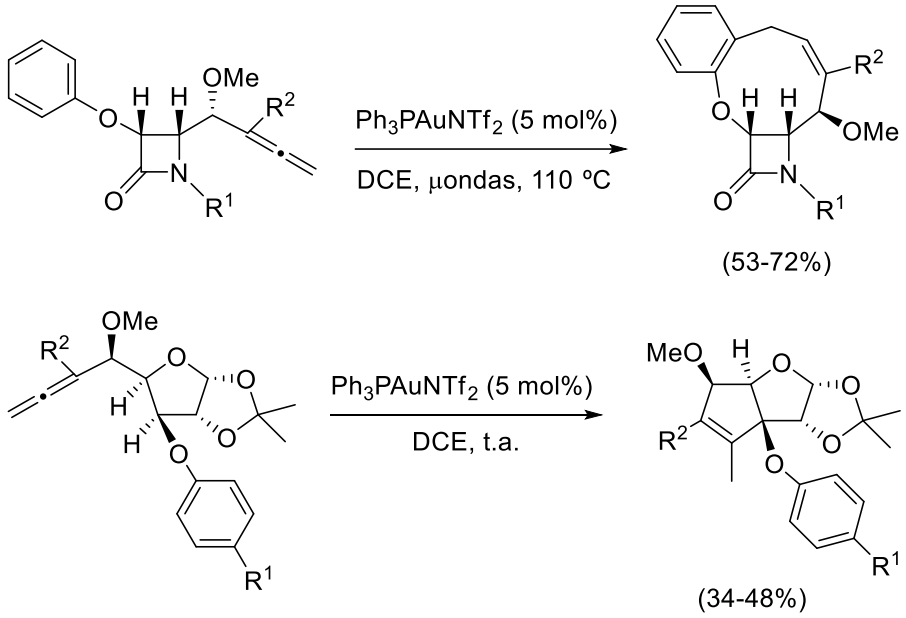
Finalmente, los compuestos fluorados presentan una importante actividad biológica gracias a su alta lipofilia y estabilidad metabólica. Asimismo, la desaromatización de indoles ha ganado especial importancia en Síntesis Orgánica debido a la alta bioactividad que presentan las indolinas resultantes. Por este motivo, en los últimos años se han descrito un gran número de métodos de fluoración de indoles funcionalizados, que permiten obtener de manera directa una gran variedad de indolinas fluoradas.

XIII.2.2. Objetivos

El objetivo general de esta tesis doctoral es el desarrollo de nuevas reacciones de ciclación y transposición de alenos y [3]-cumulenos catalizadas por metales para la preparación de compuestos estructuralmente novedosos. En particular, el presente trabajo se ha centrado en: i) desarrollar nuevas reacciones de carbociclación de alenos unidos a núcleos de importancia biológica como el anillo β-lactámico, el azúcar glucofuranosa o el indol; ii) describir nuevas reacciones de transposición de alenos; iii) estudiar la reactividad de [3]-cumulenoles mediante catálisis metálica.

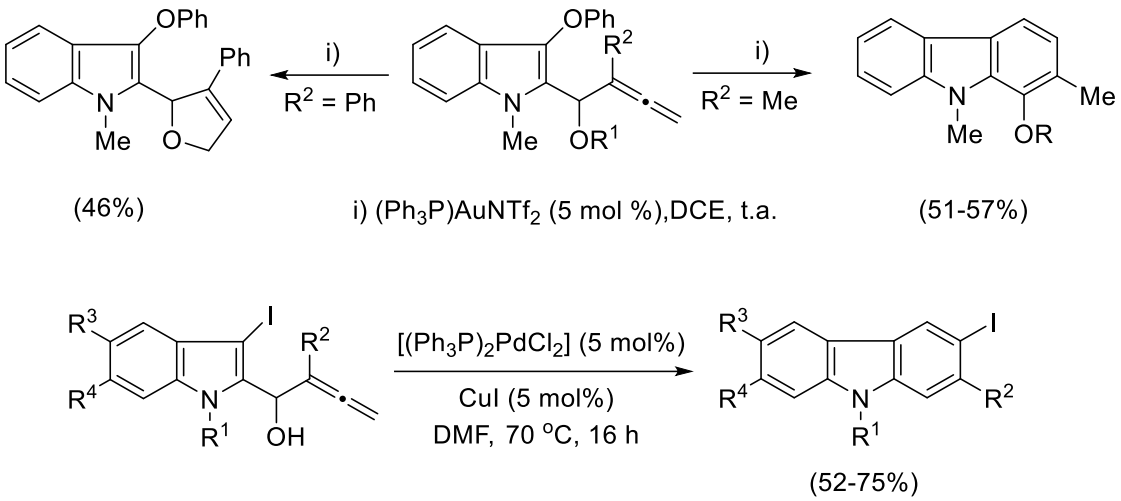
XIII.2.3. Resultados

En primer lugar se ha descrito una reacción de carbociclación 9-*endo* de alenil arenos catalizada por oro para la preparación de benzociclos fusionados de nueve miembros a través de una reacción de hidroarilación intramolecular. Por el contrario, los alenilazúcares han dado lugar a la formación de ciclopentenos fusionados al núcleo de glucofuranosa mediante una hidroalquilación 5-*exo* poco común. Con este estudio ha quedado patente, por tanto, la importancia del núcleo unido al sustituyente alénico, ya que puede suponer un gran cambio en el mecanismo de la reacción (Esquema XIII.1)



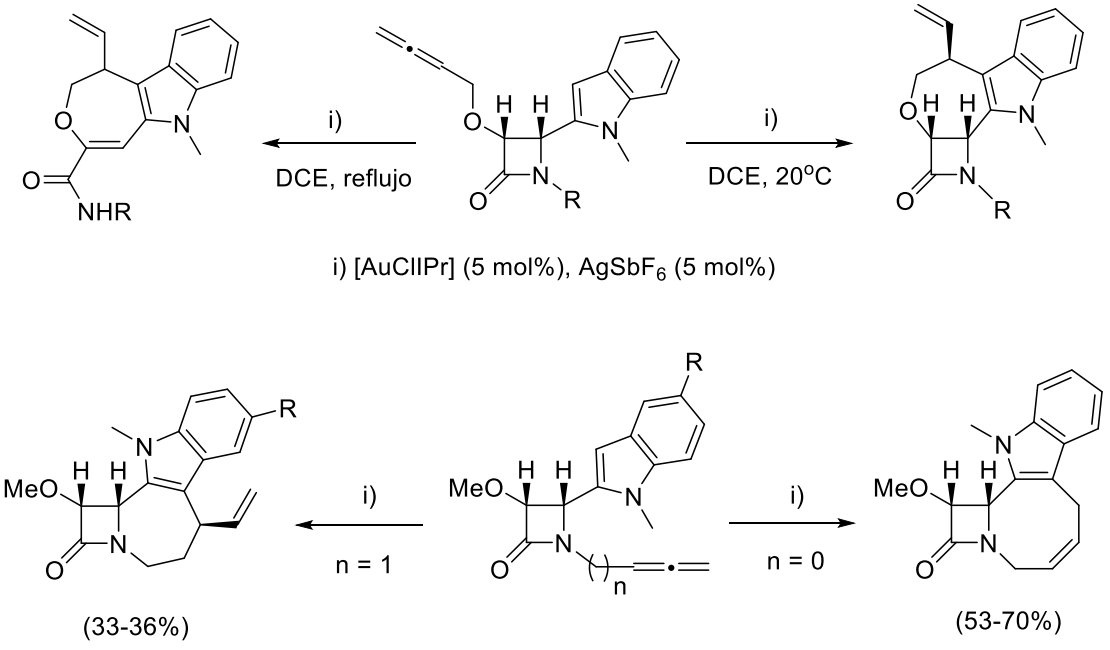
Esquema XIII.1

Se ha llevado a cabo el estudio de los diferentes patrones de reactividad de alenil indoles diferentemente sustituidos en la posición C3 del anillo indólico. Así, se ha desarrollado una migración 1,3 de yodo, no descrita previamente en la literatura, utilizando 3-yodoalenil-indoles como materiales de partida. Mientras que los 3-fenoxialenil-indoles se transformaron en los correspondientes 1-oxicarbazoles, los alenos unidos al núcleo de indol sustituido por yodo dieron lugar a 3-yodocarbazoles a través del reciclado del átomo de halógeno mediante una migración-1,3 (Esquema XIII.2).



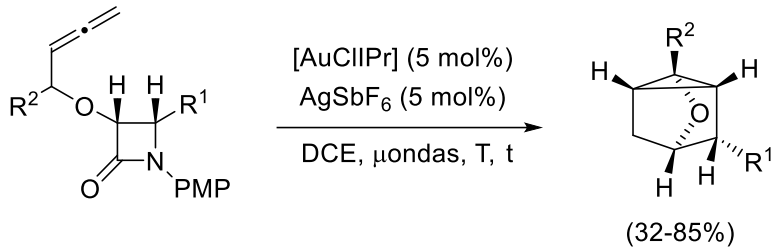
Esquema XIII.2

Por otra parte, se han descrito nuevas metodologías sintéticas de carbociclación de alenos derivados tanto del núcleo β-lactámico como indólico catalizadas por oro para la preparación de heterociclos fusionados con altos niveles de estereo- y regioselectividad (Esquema XIII.3). Asimismo, se ha descrito un nuevo proceso dominó de hidroarilación alénica seguido de ruptura del enlace N1–C4 β-lactámico catalizado por oro.



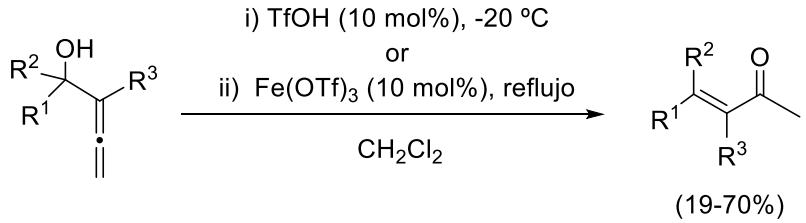
Esquema XIII.3

Se ha desarrollado una síntesis diastereoselectiva de compuestos tensionados tipo caja a través de una novedosa e inesperada reactividad catalizada por oro de alenil-β-lactamas diferentemente sustituidas (Esquema XIII.4). Tanto los resultados experimentales como los cálculos DFT realizados apoyan la participación de un intermedio (viniloxi)buta-1,2-dieno, resultante de la ruptura de los enlaces N1–C4 y C2–C3 del anillo β-lactámico.



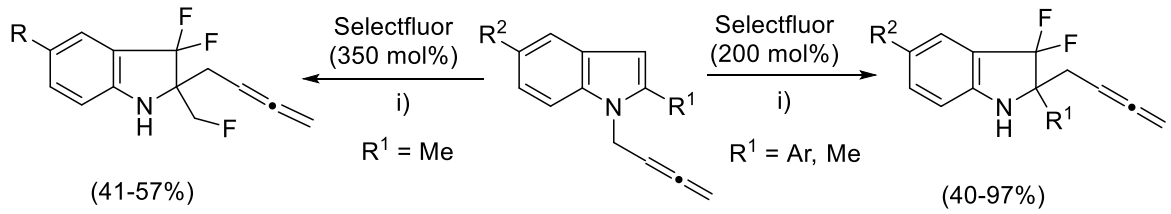
Esquema XIII.4

Teniendo en cuenta la disponibilidad y la bondad medioambiental de las sales de hierro, se ha desarrollado una nueva metodología simple y directa de preparación de cetonas α,β-insaturadas a través de un reagrupamiento tipo Meyer-Schuster de α-alenoles catalizado por hierro o protones (Esquema XIII.5).



Esquema XIII.5

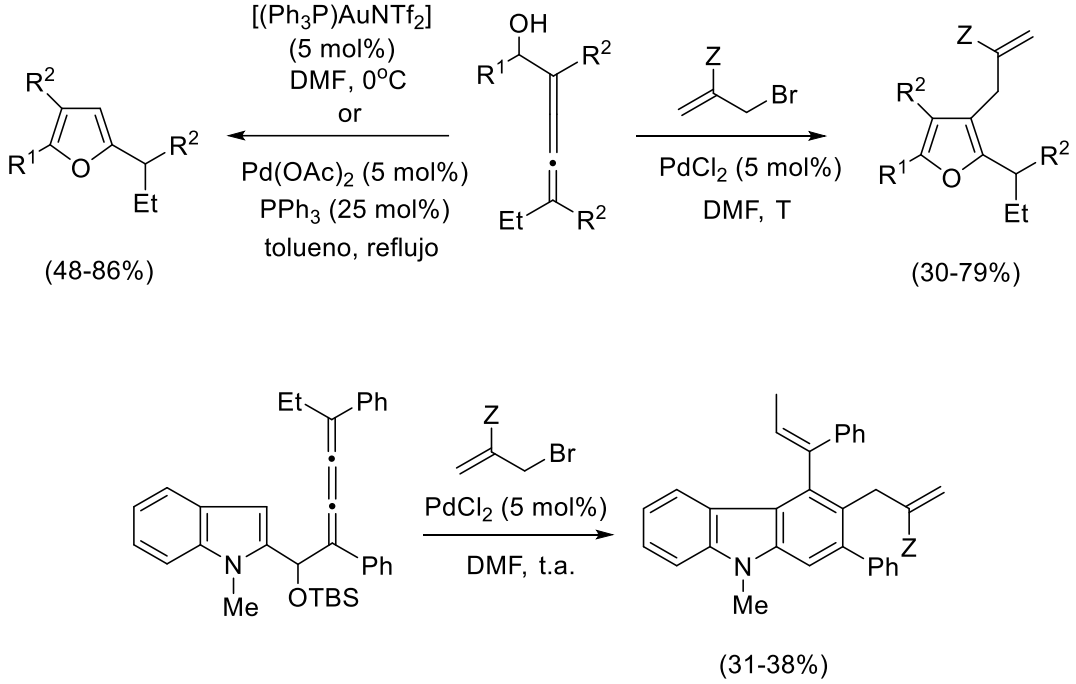
Además, debido al interés de los compuestos fluorados, así como de las indolinas, se ha descrito un nuevo método de síntesis de di- y trifluoroindolinas, a partir de *N*-alenil-indoles utilizando Selectfluor y catálisis de hierro (Esquema XIII.6).



i) $Fe(OTf)_3$ (5 mol%), $NaHCO_3$ (200 mol%), CH_3CN, t.a. o 0 ºC

Esquema XIII.6

Por último, se ha estudiado la reactividad de los [3]-cumulenos, análogos superiores a los alenos. De esta forma, se ha descrito la preparación controlada tanto de furanos tri- y tetrasustituidos como de carbazoles a través de reacciones de ciclación quimio y regioselectivas catalizadas por oro o paladio (Esquema XIII.7).



Esquema XIII.7

XIII.2.4. Conclusiones

En el presente trabajo se han desarrollado diferentes reacciones de ciclación y funcionalización de alenos y cumulenos utilizando catálisis metálica, para la preparación de compuestos con estructuras novedosas y/o potencial actividad biológica. Las metodologías descritas representan ejemplos de construcción eficiente de nuevos compuestos heterocíclicos a través de procesos sencillos, quimio- y regioselectivos.

XIV. ANEXOS

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Gold-catalysed tuning of reactivity in allenes: 9-*endo* hydroarylation *versus* formal 5-*exo* hydroalkylation†

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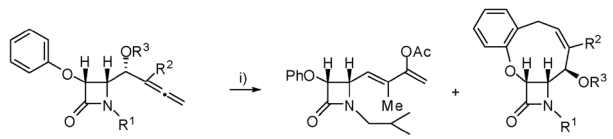
The divergent gold-catalysed reactivity (C_{sp^2}–H *versus* C_{sp^3}–H) of aryloxy-tethered allenes has been uncovered.

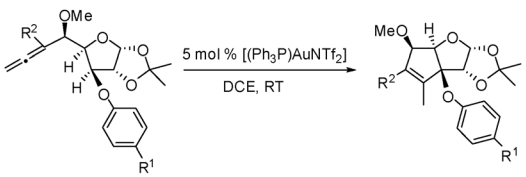
The preparation of medium-sized ring polycycles through selective C–H bond activation is a big challenge. In this regard, the gold-catalysed intramolecular hydroarylation of allenes[1] may be a possible solution to produce eight- or nine-membered carbocycles, although this achievement has not yet been accomplished. We present here an unprecedented Au-catalyzed 9-*endo* carbocyclization of aryl allenes as a powerful synthetic tool to obtain novel nine-membered annulated β-lactam derivatives.[2] In addition, it is shown that the outcome of the reaction (9-*endo* hydroarylation *versus* formal 5-*exo* hydroalkylation) can be modulated by the allene tether.

To explore the reactivity of (aryl)allene-tethered 2-azetidinones **1** towards hydroarylation, we selected acetate **1a** as a model substrate. As a first try, we were happy to notice that although the reaction of derivative **1a** afforded dienol ester **2a** as a major component (34% isolated yield), the intramolecular hydroarylation adduct **3a** was also isolated as a minor component (13%) (Scheme 1). Thus, in order to prevent the [3,3]-sigmatropic rearrangement involving the acetate group,[3] the hydroxy functionality was protected in the form of methyl ether. Fortunately, treatment of allene **1b** with [$(Ph_3P)AuNTf_2$] in 1,2-dichloroethane at room temperature gave full conversion; benzo[*b*]oxonine **3b** being isolated in 51% yield in a totally selective fashion (Scheme 1).[4] Clearly, applying microwave irradiation and using deactivated silica gel during purification resulted in an increased 72% yield for adduct **3b**. Similar figures were observed for tricyclic products **3c–h** without harming the sensitive β-lactam ring (Scheme 1). Remarkably, this rare 9-*endo* carbocyclization reaction was the only operative cyclization mode.



Scheme 1 Controlled intramolecular gold-catalysed hydroarylation of allenyl-tethered arenes **1a–h**. (i) 5 mol% [$(Ph_3P)AuNTf_2$], DCE, μwave, 110 °C (RT for **1a**). Ac = COMe. Tf = triflyl. DCE = 1,2-dichloroethane.

We also decided to undertake a study of the potential use of more diverse substrates in this novel allene hydroarylation mode. Thus, (aryloxy)allenyl-tethered sugars **4a–e** were studied by using the optimum reaction conditions obtained for (aryloxy)allenyl-tethered 2-azetidinones **1b–h**. Remarkably, we found a divergent reactivity compared with the transformation found with allenes **1**; instead of the expected hydroarylation adducts, tricycles **5** arising from a rare 5-*exo* hydroalkylation were obtained (Scheme 2). Notably, the direct and selective functionalization of an otherwise inactive C_{sp^3}–H bond has been achieved.[5] Besides, regioselectivity can be completely



Scheme 2 Controlled intramolecular formal 5-*exo* hydroalkylation reaction of allenyl-tethered arenes **4a–e** under gold-catalysed conditions.

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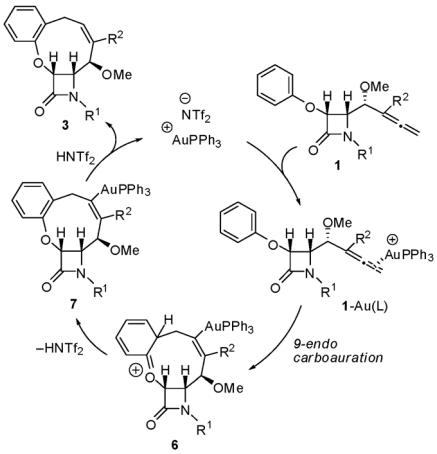
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data for new compounds, and copies of NMR spectra. See DOI: 10.1039/c2cc37872h



Scheme 3 Mechanistic explanation for the gold-catalysed hydroarylation of allenyl-tethered oxyarenes **1**.

reversed by using the sugar derivative, thus favouring the cyclization of the aryloxy ether group toward the central allene carbon over the cyclization towards the terminal allene carbon. The reaction of allenes **4** did take place with complete stereoselectivity, representing a selective method to afford fused cyclopentenes **5** bearing a quaternary stereocenter.[6] Complete conversion was observed by TLC and ^{1}H NMR analysis of the crude reaction mixtures of allenols **4**, and no side-products from isomerisation or polymerisation reactions were detected. Unfortunately, some decomposition was observed on sensitive tricycles **5** during purification by flash chromatography, which may be responsible for the moderate isolated yields.

A possible pathway for the gold-catalysed achievement of tricycles **3** from allenyl-tethered arenes **1** may initially involve the formation of a complex **1**–Au(L) through coordination of the gold salt to the distal allenic double bond. Next, chemo- and regioselective 9-*endo* carboauration forms species **6**. Attack from the activated 2-position of the arene occurs as a result of the stability of the intermediate oxonium cation type **6**. Loss of proton generates neutral species **7**, which followed by protonolysis of the carbon–gold bond afforded fused nine-membered cycles **3** with concurrent regeneration of the gold catalyst (Scheme 3).

Density functional theory (DFT) calculations have been carried out to gain more insight into the reaction mechanism of the abovediscussed gold-catalysed 9-*endo* hydroarylation reaction. The corresponding computed reaction profile of the model allenyl-β-lactam reactant **1M** with [(Me$_3$P)AuNTf$_2$] as catalyst is illustrated in Fig. 1, which shows the corresponding free energies in CH_2Cl_2 solution (PCM-M06/def2-SVP//PCM-B3LYP/def2-SVP level). Our calculations suggest that the reaction starts with the exergonic coordination of the AuPMe$_3^+$ catalyst to the distal double bond of the allenic moiety of **1M** (ΔG_{298} = −9.4 kcal mol^{-1}). Then, the 9-*endo* carbocyclization reaction to produce the nine-membered ring tricyclic intermediate **2M** occurs through the transition state **TS1**. This saddle point is associated with the nucleophilic addition of the activated *ortho*-carbon atom to the electrophilic gold complex. Although the activation barrier of this model reaction is relatively high ($\Delta G_{a,298}$ = 29.9 kcal mol^{-1}),[7] this process is kinetically and thermodynamically favoured over the corresponding carbocyclization reactions leading to 7- or 8-membered ring intermediates.[8] This result is in agreement with the exclusive formation of nine-membered ring tricyclic compounds **3**, as experimentally observed. Intermediate **2M** is then transformed into the neutral complex **4M** *via* the initially formed complex **3M** (where the NTf$_2^-$ anion is weakly bonded to **2M**) through transition state **TS2**. The latter saddle point is associated with

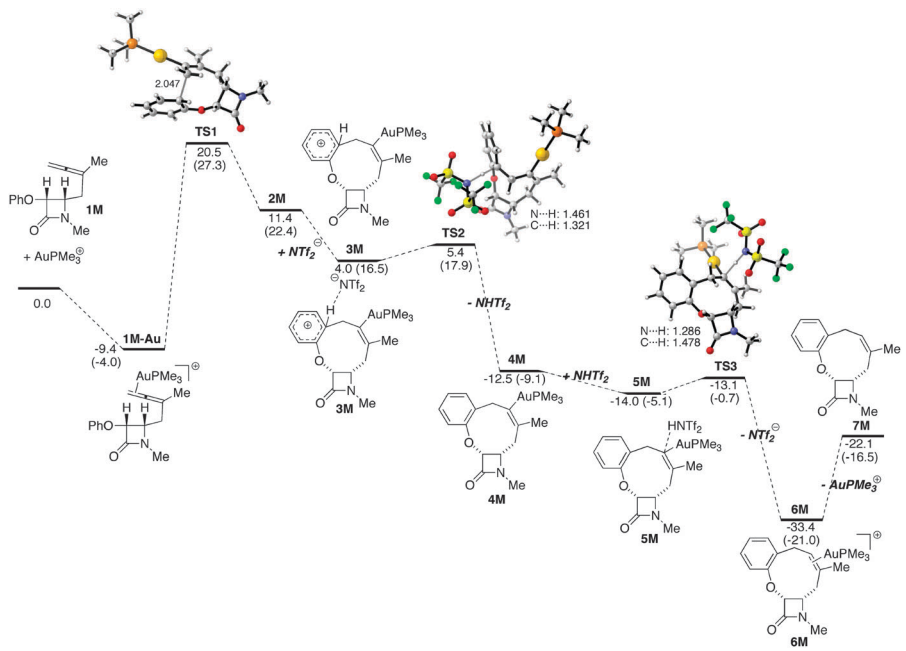
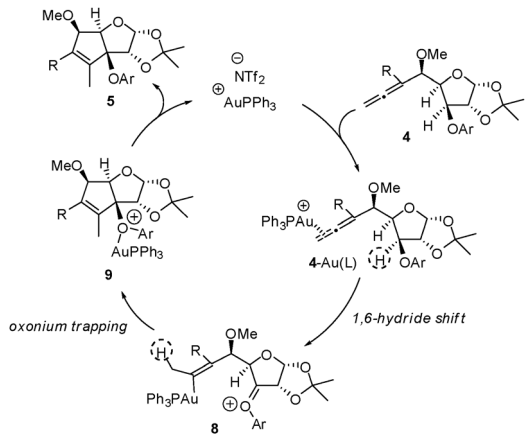


Fig. 1 Computed reaction profile for the reaction of allenyl-β-lactam **1M** and [(PMe$_3$)AuNTf$_2$] catalyst.[11]



Scheme 4 Mechanistic explanation for the gold-catalyzed formal 5-*exo* hydroalkylation of allenyl-tethered oxyarenes **4**.

the easy and exergonic proton abstraction in **2M** by the NTf_2^- anion ($\Delta G_{a,298}$ = 1.4 kcal mol^{-1} and ΔG_{298} = −16.9 kcal mol^{-1}, from **3M**). The addition of the readily formed $NHTf_2$ to **4M** forms complex **5M**, which evolves into complex **6M** *via* **TS3** (associated with the protonolysis reaction of the carbon–gold bond). The latter process is also highly exergonic (ΔG_{298} = −19.4 kcal mol^{-1}) and proceeds with a very low activation barrier ($\Delta G_{a,298}$ = 0.9 kcal mol^{-1}).[9,10] Thus, it can be concluded that the initial 9-*endo* carbocyclization reaction constitutes the bottle-neck of the process in view of the corresponding endergonicity and relatively high activation barrier. Finally, the reaction ends up with the release of the $AuPMe_3^+$ catalyst, which is coordinated to the endocyclic C=C double bond of **6M**, to produce the final tricyclic species **7M**.

A mechanistic rationale for the gold-catalysed conversion of allenyl-tethered sugars **4** into fused cyclopentenes **5** is more intricate. It is worth noting that the cyclization affords adducts **5** from an allene umpolung hydrofunctionalization instead of that from the usually preferred conventional hydrofunctionalization. The pathway proposed in Scheme 4 looks valid for the formation of tricycles of type **5**. It could be presumed that the initially formed gold complex **4**–Au(L), through coordination of the gold salt to the distal allenic double bond, undergoes a 1,6-hydride shift (rare transfer of hydride *versus* normal nucleophilic group attack), giving rise to the oxonium species **8**. Intramolecular trapping of the oxonium group by the alkenylgold moiety in intermediates **8** generates cationic species **9**, through formal 5-*exo* hydroalkylation. Finally, demetalation yields fused cyclopentenes **5** and regenerates the gold catalyst (Scheme 4).

Preliminary DFT calculations on the model (aryloxy)allenyl-tethered sugar species **8M** (see Fig. S3 in the ESI†) indicate that the direct 1,6-hydride shift from the distal double bond-coordinated complex **8M–Au** occurs with a relatively high activation barrier ($\Delta G_{a,298}$ = 37.7 kcal mol^{-1}, that is 25.2 kcal mol^{-1} above the separate reactants **8M** and $AuPMe_3^+$). This step is followed by the highly exergonic C–C bond forming reaction (*i.e.* oxonium trapping) *via* **TS5** with an activation barrier of 26.1 kcal mol^{-1}. Further DFT calculations involving the NTf_2-mediated 1,6-hydride shift and more realistic species leading to a process more compatible with a reaction at room temperature are currently underway.

In conclusion, the divergent gold-catalysed reactivity (C_{sp^2}–H *versus* C_{sp^3}–H) of aryloxy-tethered allenes has been studied. We report herein an efficient gold-catalysed 9-*endo* carbocyclization to fused tricyclic β-lactams from easily accessible aryl allene substrates under mild conditions. In salient contrast to the reaction of (aryloxy)allenyl-tethered 2-azetidinones, the allenyl sugar derivatives provided the 5-*exo* hydroalkylation adducts as the sole products. The reactions were found to proceed with complete control of product regio- and chemoselectivity.

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Notes and references

1 For a review, see: (*a*) N. Krause and C. Winter, *Chem. Rev.*, 2011, **111**, 1994. For available reports, see: (*b*) W. Kong, C. Fu and S. Ma, *Chem.–Eur. J.*, 2011, **17**, 13134; (*c*) B. Alcaide, P. Almendros, J. M. Alonso, M. T. Quirós and P. Gadziński, *Adv. Synth. Catal.*, 2011, **353**, 1871; (*d*) R. M. Zeldin and F. D. Toste, *Chem. Sci.*, 2011, **2**, 1706; (*e*) J. Barluenga, M. Piedrafita, A. Ballesteros, A. L. Suárez-Sobrino and J. M. González, *Chem.–Eur. J.*, 2010, **16**, 11827; (*f*) W. Kong, C. Fu and S. Ma, *Eur. J. Org. Chem.*, 2010, 6545; (*g*) D. Weber, M. A. Tarselli and M. R. Gagné, *Angew. Chem., Int. Ed.*, 2009, **48**, 5733; (*h*) D. Weber and M. R. Gagné, *Org. Lett.*, 2009, **11**, 4962; (*i*) M. A. Tarselli and M. R. Gagné, *J. Org. Chem.*, 2008, **73**, 2439; (*j*) C. Park and P. H. Lee, *Org. Lett.*, 2008, **10**, 3359; (*k*) T. Watanabe, S. Ohishi, N. Fujii and H. Ohno, *Org. Lett.*, 2007, **9**, 4821; (*l*) C. Liu and R. A. Widenhoefer, *Org. Lett.*, 2007, **9**, 1935; (*m*) Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Quian and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2006, **128**, 9066; (*n*) Z. Liu, A. S. Wasmuth and S. G. Nelson, *J. Am. Chem. Soc.*, 2006, **128**, 10352.

2 β-Lactams are not only the most commonly prescribed antibacterial agents, but also exhibit some other biological activities.

3 A. K. Buzas, F. M. Istrate and F. Gagosz, *Org. Lett.*, 2007, **9**, 985.

4 A screening of different gold complexes was undertaken. $AuCl_3$, AuCl, and [(PPh_3)AuOTf] all failed to catalyse this reaction. The cyclizations of allene **1b** using [$IPrAuSbF_6$] or [$IPrAuBF_4$] catalysts did not lead to complete consumption of starting **1b**, providing adduct **3b** in very low yield. Change in the nature of the phosphine in the gold pre-catalyst has little effect on the reaction, because replacing [$(Ph_3P)AuNTf_2$] by [$P(t\text{Bu})_2(o\text{-biphenyl})AuNTf_2$] did not show any appreciable difference.

5 For a 1,5-hydride shift from benzyl ethers and tetrahydrofurans onto allenes, see: B. Bolte and F. Gagosz, *J. Am. Chem. Soc.*, 2011, **133**, 7696.

6 Biologically active heliconols having the 2*H*-cyclopenta[*b*]furan core of fused compounds **5** have been isolated from natural sources.

7 The barrier energy is reduced to 25.8 kcal mol^{-1} when the more realistic $AuPPh_3^+$ catalyst is used (see Fig. S1 in the ESI†).

8 See Fig. S2 in the ESI†.

9 In sharp contrast, the corresponding proton abstraction and protonolysis reactions in the 7-membered ring formation process proceed with much higher activation barriers ($\Delta G_{a,298}$ = 16.9 and 37.1 kcal mol^{-1}). This makes the 7-membered ring formation a non-competitive transformation. See Fig. S2 in the ESI†.

10 The easiness of the protonolysis reaction is in contrast to related processes whose computed activation barriers are much higher. See: (*a*) B. Alcaide, P. Almendros, T. Martínez del Campo and I. Fernández, *Chem. Commun.*, 2011, **47**, 9054; (*b*) B. Alcaide, P. Almendros, T. Martínez del Campo, E. Soriano and J. L. Marco-Contelles, *Chem.–Eur. J.*, 2009, **15**, 1909.

11 Plain values indicate the relative free energies (ΔG, at 298 K) at the PCM(CH_2Cl_2)-M06/def2-SVP//PCM(CH_2Cl_2)-B3LYP/def2-SVP level, whereas values in parentheses are computed at the PCM(CH_2Cl_2)-B3LYP/def2-SVP level. Bond distances of the transition states are given in angstroms.

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Iodine recycling *via* 1,3-migration in iodoindoles under metal catalysis†

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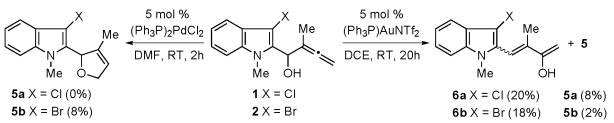
3-Substituted (indol-2-yl)-α-allenols show divergent patterns of reactivity under metal catalysis. An unprecedented intramolecular 1,3-iodine migration is described.

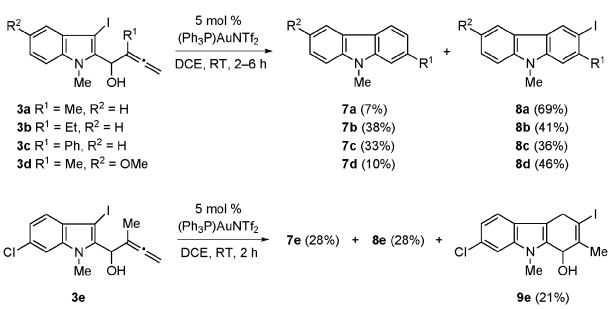
Despite the fact that aryl halides are used in many metal-catalysed synthetic developments,[1] low atom economy is a disadvantage because the heteroatom is usually eliminated. A great challenge to be accomplished is the conversion of readily available aryl halides into halogenated products in which the heteroatom is not eliminated but reintegrated into the reaction product.[2] Recently, we have successfully reported metal-catalysed carbocyclizations of 3-unsubstituted (indol-2-yl)-α-allenols for the direct preparation of the relevant carbazole nucleus.[3] We envisioned that a different behaviour of indole-tethered allenols might be achieved if the reactive C3-indole position was substituted with an activating group. Herein, we report our findings starting from 3-halo- and 3-phenoxy-(indol-2-yl)-α-allenols **1–4**.

To explore the possibility of a 1,3-heteroatom migration, chloro- and bromoallenes **1** and **2** were initially chosen. Unfortunately, 2,5-dihydrofurans **5**, formed through the usual palladium-catalysed oxycyclization reaction,[4] and dienes **6**, formed *via* gold-catalysed rearrangement, were the only products formed (Scheme 1). The above experiments suggested that the halide recycling is troublesome.

We thought that the use of an iodo-alkenyl rather than a Cl(Br)-species to initiate the allene functionalization could make the halogen recycling reaction possible.[2] We first investigated the reactions of allenols **3a–e** bearing a C3-iodosubstituent at the indole nucleus under our previously optimized gold-catalysed conditions. Interestingly, a separable mixture of carbazoles **7a–e** and iodocarbazoles **8a–e** was obtained (Scheme 2). The iodocyclization of allenol **3a** afforded the corresponding 3-iodocarbazole **8a** in 69% yield and carbazole **7a** in 7% yield. Diminished iodocarbazole/carbazole selectivity of ethyl- and phenyl-substituted reactants **3b** and **3c**, were observed with respect to methyl-substituted allenes **3a**, **3d** and **3e**. In addition to the expected carbazole **7e** and iodocarbazole **8e**, 1-hydroxy-3-iododihydrocarbazole **9e** was also formed from the chloroderivative **3e**. It should be noted, that in our previous work on metal-catalyzed carbocyclization of 3-unsubstituted (indol-2-yl)-α-allenols, we were not able to obtain iodocarbazoles **8** by trapping the postulated organometallic intermediate with halogenated reagents.[3a] Considering the versatility of organic iodides in chemical transformations, iodinated carbazoles **8** are potentially interesting building blocks for further manipulation.[5] The structure of



Scheme 1 Metal-catalysed reactions of 3-chloro/bromo (indol-2-yl)-α-allenols **1** and **2**.



Scheme 2 Synthesis of carbazoles **7**, 3-iodocarbazoles **8**, and 3-iododihydrocarbazole **9e** through carbocyclization/halogen recycling reactions of iodoallenols **3** under gold catalysis.

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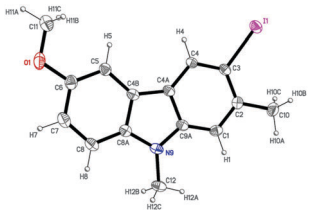
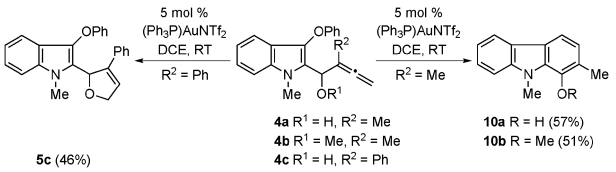


Fig. 1 ORTEP drawing of 3-iodocarbazole **8d**.

3-iodocarbazole **8d** was unambiguously confirmed with the help of X-ray diffraction analysis on suitable crystals of this compound (Fig. 1).[6]

In an attempt to improve the iodocarbocyclization efficiency under related metal-catalysed conditions, we screened a different catalytic system such as $PdCl_2(PPh_3)_2$ in the reaction with 3-iodo-(indol-2-yl)-buta-2,3-dienol **3a**. While the Pd-catalysed reaction proceeded with an optimal product distribution (a 100 : 0 ratio of the desired 1,3-iodine migration product to the non-iodinated carbazole), the isolated yield of 3-iodocarbazole **8a** was poor (38%). Therefore, we moved to a different catalytic system. Finally, compound **8a** was prepared in acceptable yield (61%) *via* the reaction of **3a** in the presence of a Pd–Cu bimetallic system in DMF. Nicely, indoles **3a**, **3e**, **3f** and **3h**, bearing a methyl substituent on the allene moiety, exclusively furnished 3-iodocarbazoles **8a**, **8e**, **8f** and **8h** (Scheme 3). Unfortunately, attempts to use phenyl-substituted substrates **3c** and **3g** proved to be unsuccessful for the construction of the corresponding iodocarbazoles, possibly because of both unfavourable steric factors as well as a direct interaction of the π-aromatic system with the metal center from the catalyst. In addition to atom economy and bond-forming efficiency, the above metal-catalysed cases, shown in Schemes 2 and 3, may be considered as examples of the rare recycling of halogen groups *via* 1,3-halogen migration.[7]

Next, the annulation of 3-phenoxy-(indol-2-yl)-α-allenols **4** was examined (Scheme 4). To test the reactivity of allenes **4**, we started the initial investigation on the gold-catalysed reaction of allene **4a** under otherwise identical reaction conditions used for its iodo-counterpart **3a**. Interestingly, it was found that substrate **4a** was exclusively transformed into 1-hydroxycarbazole **10a** (Scheme 4). This interesting transformation can be explained through a gold-catalysed allenic carbocyclization with concomitant hydrodephenoxylation (see below). Thus, it was found that the synthesis of structurally interesting 1-oxygenated carbazoles could be controlled by the C3-substituent on the indole ring in allenes of type **1–4**. Next, 3-phenoxy-(indol-2-yl) allenes **4b** and **4c** were examined in this reaction (Scheme 4). Allene **4b** was successfully converted to



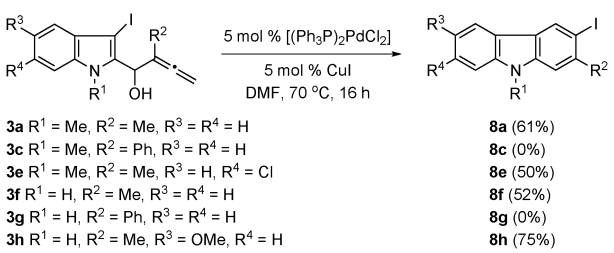
Scheme 4 Synthesis of 1-oxygenated carbazoles **10** through carbocyclization/hydrodephenoxylation reaction of phenoxyallenols **4** under gold catalysis.

1-methoxycarbazole **10b** in fair yield in the presence of Gagosz's catalyst.[8] In contrast, phenyl-substituted allene **4c** could not lead to the formation of the corresponding 1-hydroxycarbazole, affording instead the 2,5-dihydrofuran **5c**. Hence, the hydroxy group in phenyl-substituted 3-phenoxy-(indol-2-yl)-α-allenol **4c** exclusively undergoes the 5-*endo* oxycyclization reaction, instead of 6-*endo* carbocyclization.

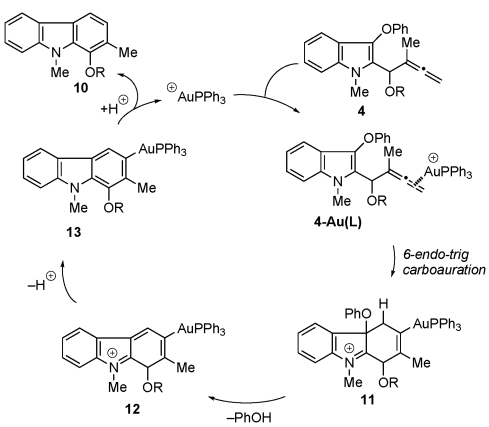
A possible pathway[9] for the gold-catalysed generation of 1-oxygenated carbazoles **10** is outlined in Scheme 5. Initially, the formation of a complex **4**-Au(L) through coordination of the gold salt to the distal allenic double bond may be involved. Species **4**-Au(L) undergoes an intramolecular chemo- and regioselective 6-*endo*-trig carbocyclization reaction to produce the auratetrahydrocarbazole **11**. This nucleophilic attack from the C3-indole site occurs as a result of the stability of the intermediate iminium type cation **11**. Next, a phenol elimination[10] step occurs in tricycle **11** through C3–OPh bond cleavage to generate the dihydrocarbazolium **12**. Aromatization by loss of proton generates neutral species **13**, which followed by protonolysis of the carbon–gold bond afforded 1-oxygenated carbazoles **10** with concurrent regeneration of the gold catalyst (Scheme 5).

Density functional theory (DFT) calculations have been carried out at the PCM-M06/def2-SVP//B3LYP/def2-SVP level[11] to gain more insight into the reaction mechanism of the above discussed transition metal-catalysed carbocyclization/halogen recycling reactions of iodoallenols **3**. Thus, the corresponding computed reaction profile of the reaction of allenol **3a** and the model catalyst $AuPMe_3^+$ is shown in Fig. 2, which shows the respective free energies, ΔG_{298}, in dichloroethane solution.

The process begins with the exergonic coordination of the catalyst to the distal allenic double bond of **3a** to form intermediate **INT1** ($\Delta G_{R,298} = -11.9$ kcal mol^{-1}). Then, the nucleophilic attack of



Scheme 3 Synthesis of 3-iodocarbazoles **8** through carbocyclization/halogen recycling reactions of iodoallenols **3** under palladium catalysis.



Scheme 5 Mechanistic explanation for the Au(I)-catalysed synthesis of 1-oxygenated carbazoles **10** from phenoxyallenols **4**.

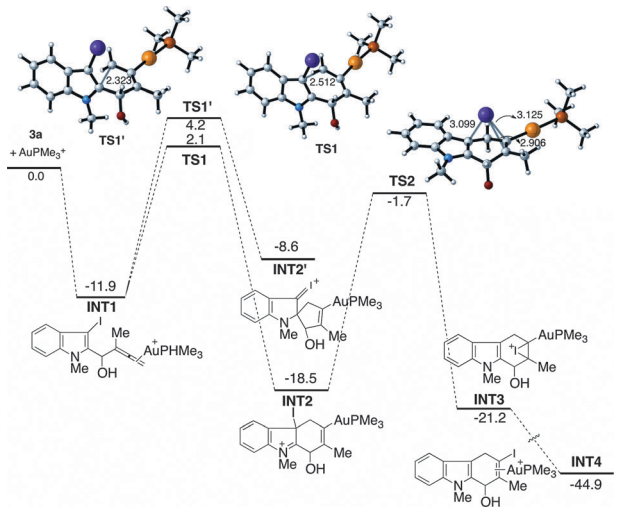


Fig. 2 Computed reaction profile (PCM(dichloroethane)-M06/def2-SVP//B3LYP/def2-SVP level) for the reaction between **3a** and $AuPMe_3^+$. Relative free energies are given in kcal mol^{-1} and bond distances in the transition states in angstroms.

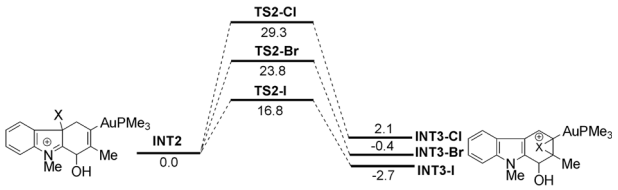


Fig. 3 Comparison of the migratory aptitude of halogen atoms in the proposed 1,3-shift. Relative free energies are given in kcal mol^{-1}. All data have been computed at the PCM(dichloroethane)-M06/def2-SVP//B3LYP/def2-SVP level.

the C3-indole position on the gold(I)-activated double-bond delivers auratetrahydrocarbazole **INT2**. This carbocyclization reaction occurs through the transition state **TS1** with an activation barrier of $\Delta G^{\neq}_{298}$ = 14.0 kcal mol^{-1} in an exergonic transformation ($\Delta G_{R,298}$ = −6.6 kcal mol^{-1}), which is compatible with the process at room temperature. Alternatively, it has been recently suggested that species related to **INT2** may be formed from spiranic species **INT2′** through a 1,2-migration reaction.[12] However, our calculations indicate that the initial formation of **INT2′** *via* **TS1′**, a saddle point associated with the C2-indole nucleophilic attack, is kinetically and thermodynamically less favoured than the process involving **TS1**, which makes the alternative pathway non-competitive. The origins of this behaviour are found in the well-known activation of the C3-carbon atom by the nitrogen atom of the indole.[13] Once **INT2** is formed, it is transformed into the iodonium species **INT3** through **TS2** (an activation barrier of $\Delta G^{\neq}_{298}$ = 16.8 kcal mol^{-1}) in an exergonic process ($\Delta G_{R,298}$ = −2.7 kcal mol^{-1}). As shown in Fig. 2, **TS2** is associated with the 1,3-migration of the iodine atom to the endocyclic double bond of the adjacent six-membered ring. This step resembles that of the typical electrophilic halogen addition to alkenes. Indeed, the computed positive NBO-charge at the iodine atom in **INT3** (q = +0.35e) clearly confirms the cyclic-iodonium cation nature of this species. Therefore, this step can be viewed as an unprecedented intramolecular iodine cation addition to a metal-activated double bond. The next step of the transformation involves the liberation of the metal catalyst through formation of the corresponding iododihydrocarbazoles **9** from **INT4**. Subsequent aromatization by dehydration would produce the observed 3-iodocarbazoles **8**. Although the isolation of tricycle **9e** from the reaction of **3e** as outlined in Scheme 2 was fortuitous, the result argues in favour of the suggested reaction mechanism, because an observable intermediate of type **9** was formed.

Finally, we have also investigated why chlorine or bromine substituted allenols **1** and **2** do not undergo a similar 1,3-migration to that found for iodoallenols **3**. As clearly shown in Fig. 3, the computed activation barriers associated with the 1,3-halogen shifts involving chlorine and bromine atoms are much higher than the barrier associated with the migration of iodine ($\Delta G^{\neq}_{298}$ = 29.3 and 23.8 kcal mol^{-1} for Cl and Br, respectively). Therefore, our calculations suggest that the migratory aptitude of halogen atoms in this transition metal-mediated process follows the order I ≫ Br > Cl, which is in nice agreement with the experimental findings.[14]

In conclusion, in salient contrast to the reaction of 3-phenoxy-(indol-2-yl) allenes, which were transformed into 1-oxygenated carbazoles, 3-iodo-(indol-2-yl) allenes afforded 3-iodocarbazoles through rare recycling of halogen groups *via* 1,3-halogen migration. Besides, a computational study suggested the intermediacy of an iodonium cation species formed through an unprecedented intramolecular iodine cation addition to a metal-activated double bond.

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Notes and references

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Gold as Catalyst for the Hydroarylation and Domino Hydroarylation/N1−C4 Cleavage of β-Lactam-Tethered Allenyl Indoles

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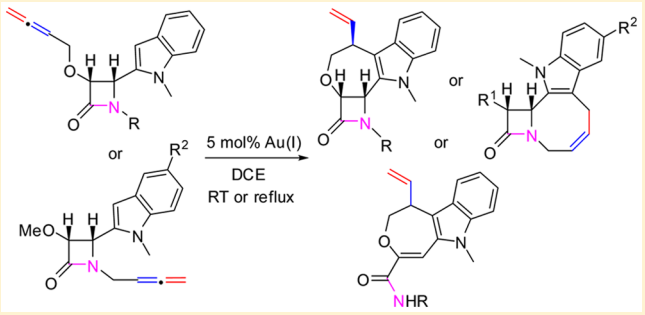
Supporting Information

ABSTRACT: Gold-catalyzed hydroarylation reaction of β-lactam-tethered allenyl indoles gives azeto-oxepino[4,5-*b*]-indol-2-ones, tetrahydroazeto-azocino[3,4-*b*]indol-2-ones, and hexahydroazeto-azepino[3,4-*b*]indol-2-ones with very high levels of stereo- and regioselectivity, the 7-*exo* and 8-*endo* carbocyclization modes by attack of the indole group toward either the internal or the terminal allene carbon, respectively, being favored. Hydroarylation across the central carbon of the allene moiety has not been detected. The controlled gold-catalyzed annulations allowed the formation of fused β-lactams without harming the sensitive four-membered heterocycle. Besides, a novel gold-catalyzed domino process, namely, the allenic hydroarylation/N1−C4 β-lactam bond breakage to afford dihydro-oxepino[4,5-*b*]indole-4-carboxamides, has been discovered.



INTRODUCTION

Of the several heterocycles, β-lactams and their derivatives attracted greater attention due to their biological activities such as antibacterial, enzyme inhibitors, neuroprotectors, and antitumorals.[1] In addition to the presence of the 2-azetidinone motif in medicinally relevant substances, the β-lactam nucleus is of great importance since 2-azetidinones display relatively high reactivity due to their strained nature, making them versatile intermediates in organic synthesis.[2] Indole derivatives have also received increasing attention in view of their biological and pharmacological activities. In accordance, efforts devoted to the synthesis of both molecular frameworks remain highly desirable.

The direct formation of C−C bonds involving C−H bond cleavage is of great interest because it offers an alternative to the conventional cross-coupling strategies.[3] On the other hand, gold complexes continue to attract considerable interest in the synthetic community due to their powerful soft Lewis acidic nature.[4] In this context, the gold-catalyzed hydroarylation reaction of allenes is an important C−C bond cyclization method.[5] Recently, the gold-catalyzed carbocyclization of allenylindoles has been explored for the preparation of carbazoles, pyridoindoles, and cyclopentaindoles.[6] However, the gold-catalyzed intramolecular hydroarylation of indole-tethered allenes to afford medium-sized rings is almost uninvestigated; and just a sole example for the preparation of a seven-membered ring fused indole has been described in literature.[7] We envisioned that β-lactam-tethered allenyl indoles may be effective substrates for this purpose. Herein, we wish to report a synthesis of tetracyclic β-lactam/indole hybrids via an allenic hydroarylation approach, together with an unanticipated gold-catalyzed N1−C4 β-lactam bond breakage.

RESULTS AND DISCUSSION

Starting materials, new β-lactam-tethered allenyl indoles **5a−f** and **6a−f** were obtained from 2-azetidinone-tethered alkynyl indoles **3a−f** and **4a−f**. β-Lactams **1** and **4** (Scheme 1) were prepared as single *cis*-diastereoisomers from imines of indole-2-carboxaldehydes through Staudinger reaction with the appropriate alkoxyacetyl chloride in the presence of Et_3N.[8] Transesterification of 3-acetoxy-2-azetidinones **1a−f** with sodium methoxide in methanol gave 3-hydroxy-2-azetidinones **2a−f**, which, by treatment with propargyl bromide under basic conditions, gave 2-azetidinone-tethered alkynyl indoles **3a−f** (Scheme 1). Terminal alkynes **3** and **4** were conveniently converted into allenes **5** and **6** (Scheme 2) by treatment with paraformaldehyde in the presence of diisopropylamine and copper(I) bromide (Crabbé reaction).[9]

Initially, we started to evaluate the intramolecular hydroarylation reaction by employing β-lactam-tethered allenyl indole **5a** as model substrate. At the outset, the use of $AuCl_3$ and AuCl was tested, but both failed to catalyze the reaction in the presence or absence of any additive (Table 1, entries 1 and 2). Interestingly, when 1-benzyl-3-(buta-2,3-dienyloxy)-4-(1-methyl-1*H*-indol-2-yl)azetidin-2-one **1a** was treated with the

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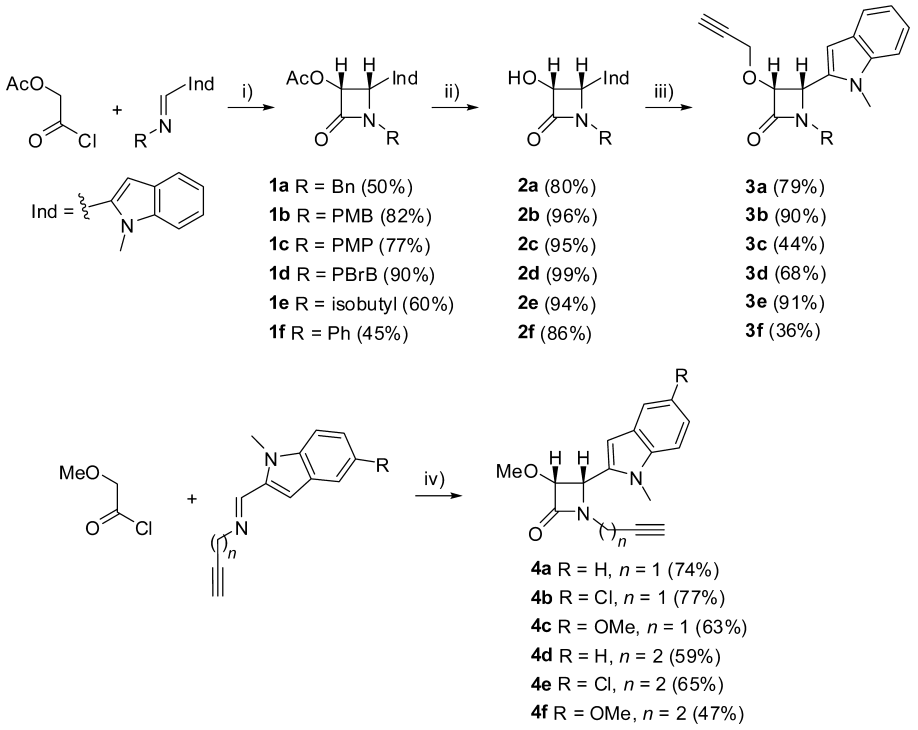
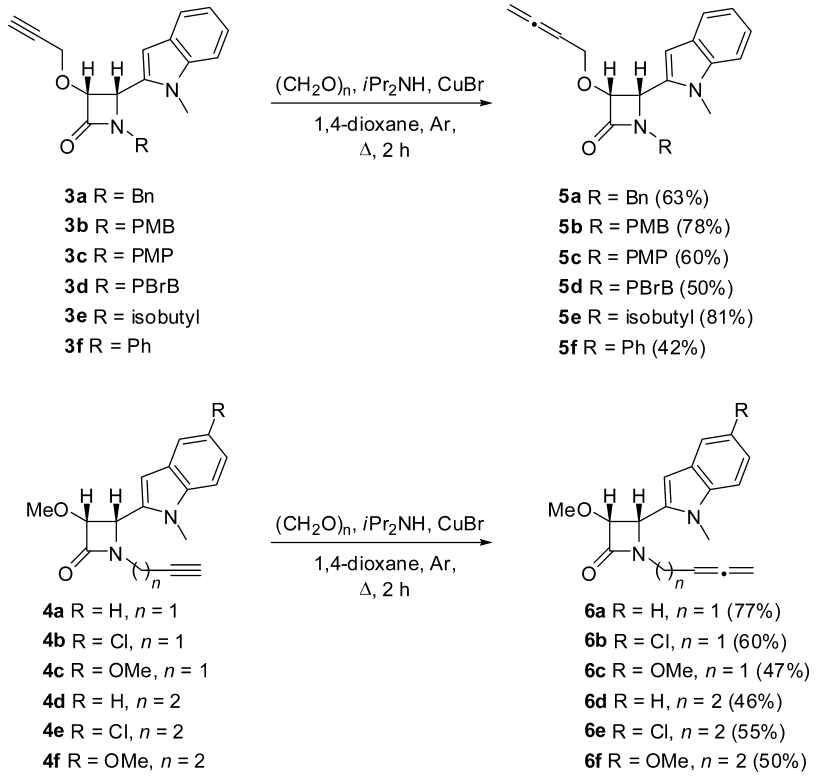
Scheme 1. Synthesis of β-Lactam-Tethered Alkynyl Indoles 3a–f and 4a–f[a]



[a]Conditions: (i) Et_3N, CH_2Cl_2, rt, 14 h. (ii) Sodium methoxide, methanol, 0 °C, 30 min. (iii) Propargyl bromide, TBAI, NaOH, CH_2Cl_2, H_2O, rt, 14 h. (iv) Et_3N, toluene, 80 °C, 2 h. PMB = 4-$MeOC_6H_4CH_2$. PMP = 4-$MeOC_6H_4$. PBrB = 4-$BrC_6H_4CH_2$. TBAI = Tetrabutylammonium bromide.

Scheme 2. Preparation of β-Lactam-Tethered Allenyl Indoles 5a–f and 6a–f



system [AuClIPr] (IPr = 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene) (5 mol %)/$AgSbF_6$ (5 mol %) in 1,2-dichloroethane (DCE) at room temperature for 5 h, indolo-oxepino β-lactam **7a** was isolated in 72% yield (Table 1, entry 5). The optimal amount of catalyst was established at 5 mol % with a ratio of Au(I) salt/Ag(I) salt of 1:1. A lower loading of catalyst had the effect of lowering the conversion for a fixed reaction time (Table 1, entry 9). A screening of solvents

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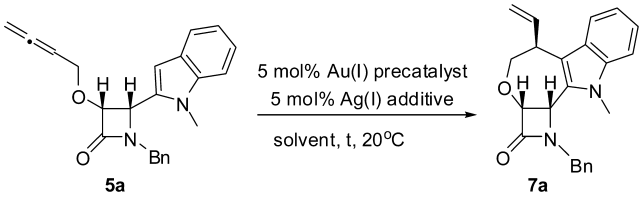
Table 1. Selective Hydroarylation Reaction of β-Lactam-Tethered Allenyl Indole 5a under Modified Gold-Catalyzed Conditions[a]



5a 7a

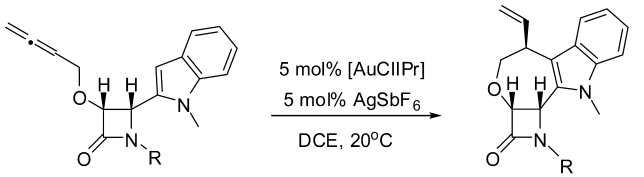
entry	Au(I) salt	Ag(I) salt	solvent/t (h)	yield[a]
1	$AuCl_3$		DCE/24	
2	AuCl		DCE/24	
3	$[AuClPPh_3]$	AgOTf	DCE/24	5
4	$[(Ph_3P)AuNTf_2]$		DCE/24	12[b]
5	[AuClIPr]	$AgSbF_6$	DCE/5	72
6	[AuClIPr]	AgOTf	DCE/1.5	43
7	[AuClIPr]	$AgBF_4$	DCE/3	62
8	[AuClIPr]	$AgNTf_2$	DCE/1.5	57
9	[AuClIPr][c]	$AgSbF_6$[c]	DCE/24	50
10	[AuClIPr]	$AgSbF_6$	dioxane/14	66
11	[AuClIPr]	$AgSbF_6$	toluene/18	60
12	[AuClIPr]	$AgSbF_6$[d]	DCE/5	69

[a]Yield of pure, isolated product with correct analytical and spectral data. [b]A byproduct in which the 2-azetidinone ring disappeared was also detected. [c]1 mol % was used. [d]10 mol % was used.

(toluene, tetrahydrofuran, 1,4-dioxane) revealed that the reaction is best performed in DCE. Other counterions have little effect on the reaction, because changing the silver salt to AgOTf, $AgBF_4$, or $AgNTf_2$ also delivered the tetracyclic product, but in lower yields (Table 1, entries 6–8). Other Au catalysts were less effective; i.e., low conversion was obtained with $[Au(OTf)PPh_3]$ while Gagosz' catalyst $[(Ph_3P)AuNTf_2]$ leads to considerable decomposition of the starting β-lactam (Table 1, entries 3 and 4).

To ascertain the efficacy and generality of the above catalytic system, various β-lactam-tethered allenyl indoles **5b–e** were treated under the optimized conditions. The N1-substituents at the β-lactam ring were varied in terms of alkyl and aryl groups. These gold-catalyzed reactions afforded products **7b–e** in yields of 63–89% as exclusive products (Scheme 3), regioisomeric adducts not even being detected as trace

Scheme 3. Synthesis of Azeto-oxepino[4,5-*b*]indol-2-ones 7b–e through Gold-Catalyzed Intramolecular Hydroarylation Reaction of β-Lactam-Tethered Allenyl Indoles 5b–e[a]



5b R = PMB
5c R = PMP
5d R = PBrB
5e R = isobutyl

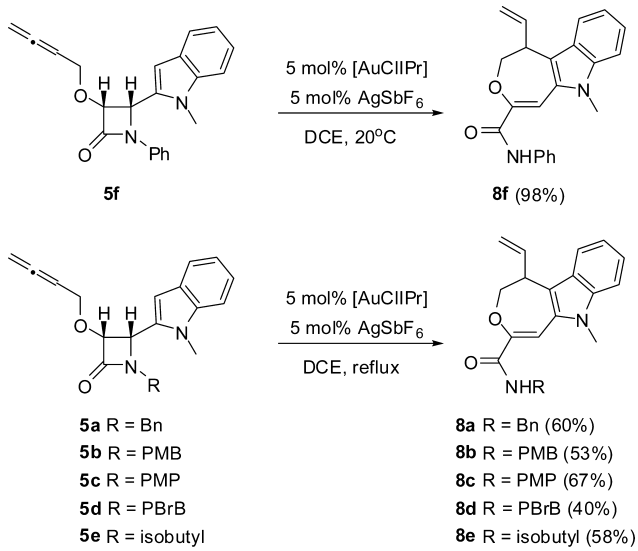
7b R = PMB (68%)
7c R = PMP (63%)
7d R = PBrB (82%)
7e R = isobutyl (89%)

[a]**7b**: 4.5 h; **7c**: 2.5 h; **7d**: 6.5 h; **7e**: 2 h. PMB = 4-$MeOC_6H_4CH_2$. PMP = 4-$MeOC_6H_4$. PBrB = 4-$BrC_6H_4CH_2$.

products. It is obvious from the experiments that, in our functionalized systems, competitive processes are not operating, the 7-*exo* carbocyclization being favored. Besides, the new stereocenter in tetracycles **7** was created in a totally stereoselective fashion. The stereochemistry of products **7** was unambiguously determined by the NOE analysis of adduct **7d**. Tetracycles **7a–e** can be considered as hybrid scaffolds as a combination of the biologically relevant β-lactam, oxepane, and fused indole frameworks.[10] Because most of the reactions were conducted on a 50–100 mg scale, it was desirable to scale up the procedure. It is worth noting that no obvious loss of yield was observed for adduct **7a** (isolated yield: 70%) when the reaction was carried out on a 500 mg scale.

We also performed the above reaction by using the N1-phenyl substrate **5f**. Surprisingly, the reaction does take a different course because the final product **8f**, which was obtained in almost quantitative yield, lacked the β-lactam ring (Scheme 4). The formation of dihydro-oxepino[4,5-*b*]indole-4-

Scheme 4. Synthesis of 1,6-Dihydro-2*H*-oxepino[4,5-*b*]indole-4-carboxamides 8a–f through Gold-Catalyzed Hydroarylation/N1–C4 β-Lactam Cleavage of β-Lactam-Tethered Allenyl Indoles 5a–f[a]



5f **8f** (98%)

5a R = Bn
5b R = PMB
5c R = PMP
5d R = PBrB
5e R = isobutyl

8a R = Bn (60%)
8b R = PMB (53%)
8c R = PMP (67%)
8d R = PBrB (40%)
8e R = isobutyl (58%)

[a]**8a**: 2 h; **8b**: 2.5 h; **8c**: 2 h; **8d**: 4 h; **8e**: 1.5 h; **8f**: 1.5 h. PMB = 4-$MeOC_6H_4CH_2$. PMP = 4-$MeOC_6H_4$. PBrB = 4-$BrC_6H_4CH_2$.

carboxamide **8f** may imply a selective breakage of the N1–C4 bond of the 2-azetidinone nucleus. We are aware of no report on the metal-catalyzed N1–C4 β-lactam bond cleavage.[11] Considering the significant effects of reaction temperature on the reactivity of the β-lactam ring,[2] new reaction conditions were optimized for substrates **5a–e**. Then, the effect of the reaction temperature on the reaction of β-lactam-tethered allenyl indole **5a** was investigated. When the reaction was performed at 40 °C, it proceeded rapidly and gave a separable mixture (1:1) of tetracycle **7a** and tricycle **8a**. To our delight, reasonable yields and total selectivity in favor of non-β-lactam adduct **8a** were achieved when the gold-catalyzed reaction was performed in DCE at reflux temperature (Scheme 4). Under the optimized reaction conditions, the substrate scope was subsequently investigated. Differently substituted β-lactam-tethered allenyl indoles **5b–e** were successfully employed to provide novel fused oxepino-indoles **8b–e** in reasonable yields

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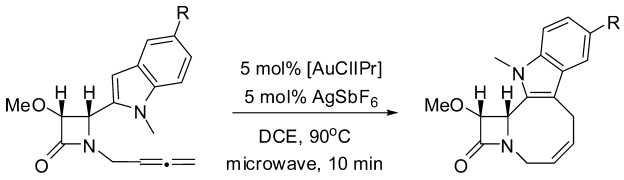
(Scheme 4). The above cascade sequence tolerated different substituents on the β-lactam nitrogen and could thus provide a good handle in building a larger α-hydroxy amide-appended indole collection. It is possible that traces of $HSbF_6$ are present in the reaction medium. A control experiment that would clarify the participation of $HSbF_6$ as the active catalyst for the β-lactam cleavage was undertaken. When indolo-oxepino β-lactam **7a** was treated with $HSbF_6{\cdot}6H_2O$ with the same catalyst ratio (5 mol %), no product **8a** was obtained, ruling out the participation of the Brønsted acid in the ring-opening process.

To assess the scope of this reaction, the allene moiety was moved from position C3 to N1, as in 1,4-tethered allenylindoles **6**. Attempts of the gold-catalyzed cyclization reaction of compounds **6** failed at room temperature. To our delight, when β-lactam-tethered allenyl indoles **6a−c** were tested as cyclization precursors applying microwave irradiation, after 10 min, it furnished the corresponding tetracycles **9a−c** as the sole isomers (Scheme 5). As shown in Scheme 4, various

Scheme 5. Synthesis of Tetrahydroazeto-azocino[3,4-*b*]indol-2-ones 9a−c through Gold-Catalyzed Intramolecular Hydroarylation Reaction of β-Lactam-Tethered Allenyl Indoles 6a−c

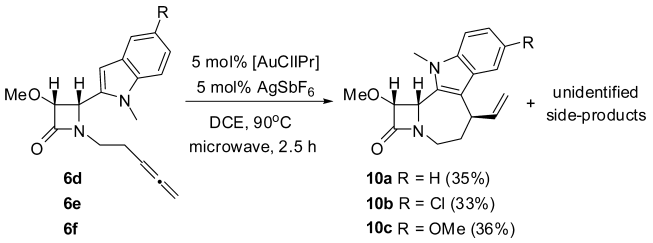


substituents with different electronic features at the indole ring showed good reactivity. Both, allenyl indoles **6** bearing electron-donating substituents (MeO) and electron-withdrawing substituents (Cl), worked well to afford the corresponding fused azocines **9**. The formation of tetrahydroazeto-azocino-[3,4-*b*]indol-2-ones **9** may be explained through an 8-*endo* carbocyclization of the indole group toward the terminal allene carbon. In this case, the gold-catalyzed annulations allowed the regioselective formation of fused β-lactams without harming the sensitive four-membered heterocycle.

We also decided to undertake a study of the potential use of more diverse substrates in this novel hydroarylation mode. Thus, β-lactam-tethered allenyl indoles **6d−f** were studied by using the optimum reaction conditions obtained for homologue *N*-allenes **6a−c**. Complete conversion was observed after prolonged exposure, but unidentified side-products from isomerization or polymerization were detected in the ^1H NMR analysis of the crude reaction mixtures. We found a divergent regioselectivity compared with the transformation found with allenes **6a−c**, because tetracycles **10a−c** arising from a 7-*exo* carbocyclization were obtained as major isomers in modest yields (Scheme 6). Competing reactions lead to the exclusion of allenyl indoles **6d−f** as efficient substrates.

A possible pathway for the gold-catalyzed synthesis of dihydro-oxepino[4,5-*b*]indole-4-carboxamides **8** from β-lactam-tethered allenyl indoles **5** may or may not involve a tetracyclic intermediate. The obtention of tetracyclic adducts **7** at room temperature (Scheme 3) leads us to propose a mechanism, which is illustrated in Scheme 7, and occurs through azeto-

Scheme 6. Synthesis of Hexahydroazeto-azepino[3,4-*b*]indol-2-ones 10a−c through Gold-Catalyzed Intramolecular Hydroarylation Reaction of β-Lactam-Tethered Allenyl Indoles 6d−f



oxepino[4,5-*b*]indol-2-one species **7**. In order to see if tetracycles **7** are able to rearrange to tricyclic carboxamides **8** under metal-free catalysis, reaction of **7a** was conducted in DCE at reflux temperature for 3 h in the absence of metallic salts. The reaction did not proceed. In contrast, reaction of **7a** with a catalytic amount of $[IPrAuSbF_6]$ under otherwise identical conditions gave the dihydro-oxepino[4,5-*b*]indole-4-carboxamide **8a** in excellent yield. The fact that β-lactam **7a** in the presence of gold(I) was converted into carboxamide **8a** suggests the decisive role of the gold salt in promoting the rearrangement reaction. Probably, initial amide carbonyl coordination to cationic gold in tetracycles **7** is followed by proton abstraction, resulting in the stabilized carbanion **13**. Then, N1−C4 β-lactam bond cleavage should occur to generate the stabilized amide carbanion **14**. Finally, protonolysis leads to the formation of tricycles **8** with concurrent regeneration of the gold catalyst.

The first step of the tandem sequence should involve the formation of complex **5**-Au(L) through coordination of the gold salt to the internal allenic double bond. Species **5**-Au(L) undergoes a chemo- and regioselective intramolecular 7-*exo*-trig carbocyclization reaction to produce the auravinyl tetracycle **11**. This nucleophilic attack from the C3-indole site occurs as a result of the stability of the intermediate iminium type cation **11**. Aromatization by loss of proton generates neutral species **12**, which, followed by protonolysis of the carbon−gold bond, liberates azeto-oxepino[4,5-*b*]indol-2-one species **7**, releasing the gold catalyst into the first catalytic cycle (Scheme 7, right catalytic cycle). Next, tetracycle **7** enters the second catalytic cycle, which is also gold-catalyzed, generating ammonium species **7**-Au(L) by formation of a N−Au bond in an electrophilic fashion. Subsequent proton (H3 at the 2-azetidinone nucleus) abstraction, with concurrent N1−C4 β-lactam bond breakage in species **13**, would form the neutral amidogold(I) species **14**. Deauration linked to proton transfer liberates carboxamides **8** with concomitant regeneration of the gold catalyst, closing the second catalytic cycle (Scheme 7, left catalytic cycle).

■ CONCLUSION

In conclusion, the present study provides the first insight into the manner in which β-lactam-tethered allenyl indoles undergo carbocyclization under gold catalysis, to afford fused tetracyclic indole-β-lactams having a central seven- or eight-membered ring. In addition, a novel domino process, the gold-catalyzed allenic hydroarylation/N1−C4 β-lactam bond breakage, was discovered.

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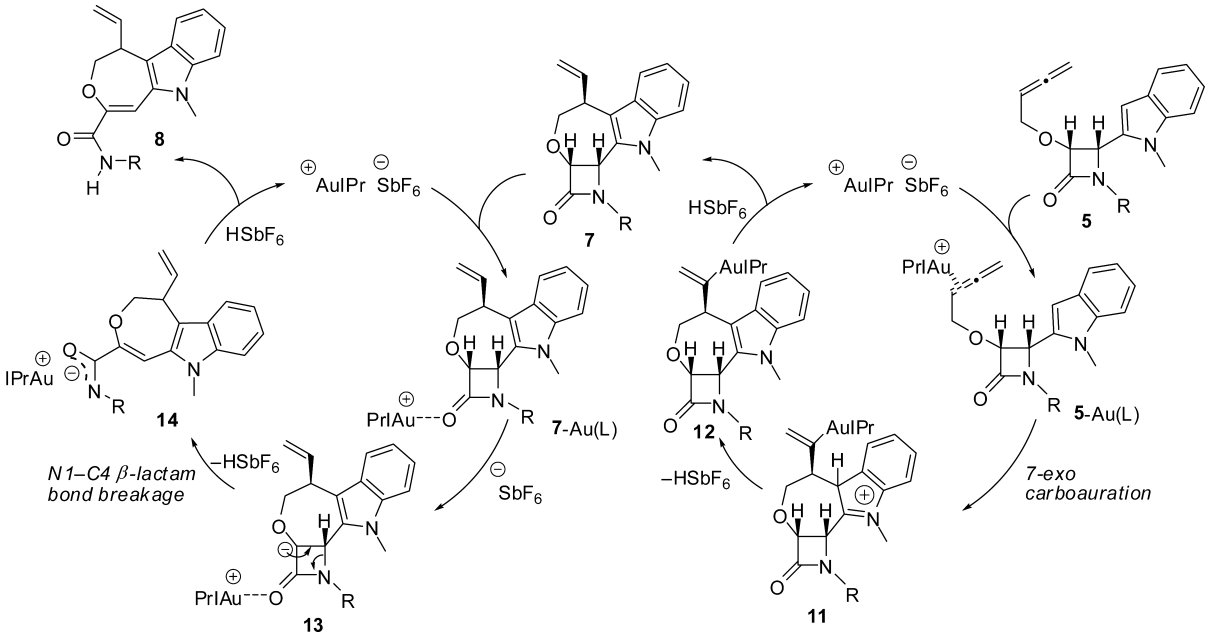
Scheme 7. Rationalization for the Gold-Catalyzed Hydroarylation/N1−C4 β-Lactam Cleavage of β-Lactam-Tethered Allenyl Indoles 5



EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded at 25 °C on a 300 MHz instrument: ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz). Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{13}C, 76.9 ppm). Low- and high-resolution mass spectra were taken on a QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES). All reported compounds are racemic. All commercially available compounds were used without further purification.

Staudinger Reaction. General Procedure for the Preparation of Acetoxy β-Lactam-Tethered Indoles 1a–f. To a solution of the corresponding imine (10.4 mmol) in dichloromethane (35 mL) and triethylamine (4.2 mL, 30 mmol) was slowly added acetoxyacetyl chloride (13 mmol) dissolved in dichloromethane (35 mL) at 0 °C under an argon atmosphere, and stirring was continued for 14 h at room temperature. Then, 15 mL of $NaHCO_3$ (aq. sat.) was added before being partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (3 × 50 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using an ethyl acetate/hexanes mixture gave analytically pure compounds **1**.

Acetoxy β-Lactam ***1a.*** From 1.0 g (4.05 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **1a** (711 mg, 50%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.82 (d, 1H, J = 7.8 Hz), 7.28 (m, 3H), 7.21 (m, 2H), 7.10 (m, 3H), 6.54 (s, 1H), 5.73 (d, 1H, J = 4.4 Hz), 4.91 (d, 1H, J = 14.7 Hz), 4.90 (d, 1H, J = 4.4 Hz), 3.99 (d, 1H, J = 14.8 Hz), 3.48 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 169.6, 164.1, 138.1, 134.3, 131.0, 129.0 (2C), 128.6 (2C), 128.2, 127.2, 122.0, 120.7, 119.8, 109.2, 102.9, 77.5, 53.8, 44.2, 29.6, 20.0; IR ($CHCl_3$, cm^{-1}): ν 2929, 1744, 1216, 734, 699; HRMS (ES): calcd for $C_{21}H_{20}N_2O_3$ $[M]^+$: 348.1474; found: 348.1486.

Acetoxy β-Lactam ***1b.*** From 746 mg (2.68 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **1b** (825 mg, 82%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.63 (d, 1H, J = 7.9 Hz), 7.28 (m, 2H), 7.14 (t, 1H, J = 7.3 Hz), 7.07 (d, 2H, J = 8.6 Hz), 6.84 (d, 2H, J = 8.6 Hz), 6.58 (s, 1H), 5.76 (d, 1H, J = 4.4 Hz), 4.93 (d, 1H, J = 4.4 Hz), 4.89 (d, 1H, J = 14.7 Hz), 3.89 (d, 1H, J = 14.7 Hz), 3.80 (s, 3H), 3.54 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 169.6, 164.0, 159.5, 138.0, 131.1, 129.9 (2C), 127.2, 126.2, 122.0, 120.7, 119.8, 114.3 (2C), 109.2, 102.9, 77.4, 55.3, 53.6, 43.6, 29.7, 20.0; IR ($CHCl_3$, cm^{-1}): ν 2923, 1753, 1220, 731; HRMS (ES): calcd for $C_{22}H_{22}N_2O_4$ $[M]^+$: 378.1580; found: 378.1574.

Acetoxy β-Lactam ***1c.*** From 917 mg (3.47 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **1c** (965 mg, 77%) as a colorless solid; mp 150−151 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.55 (d, 1H, J = 7.9 Hz), 7.33 (m, 1H), 7.32 (d, 2H, J = 9.1 Hz), 7.25 (t, 1H, J = 7.5 Hz), 7.11 (t, 1H, J = 7.4 Hz), 6.81 (d, 2H, J = 9.1 Hz), 6.52 (s, 1H), 6.01 (d, 1H, J = 4.7 Hz), 5.58 (d, 1H, J = 4.7 Hz), 3.78 (s, 3H), 3.76 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 169.6, 160.9, 156.7, 138.2, 130.5, 130.0, 127.1, 122.1, 120.8, 119.8, 118.9 (2C), 114.4 (2C), 109.1, 103.8, 76.5, 55.4 (2C), 30.1, 20.0; IR ($CHCl_3$, cm^{-1}): ν 2923, 1745, 1225, 733; HRMS (ES): calcd for $C_{21}H_{20}N_2O_4$ $[M]^+$: 364.1423; found: 364.1418.

Acetoxy β-Lactam ***1d.*** From 1.25 g (3.81 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave compound **1d** (1.46 g, 90%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.63 (d, 1H, J = 7.8 Hz), 7.46 (d, 2H, J = 8.4 Hz), 7.32 (d, 1H, J = 7.8 Hz), 7.26 (td, 1H, J = 8.2, 1.2 Hz), 7.15 (td, 1H, J = 7.3, 1.3 Hz), 7.05 (d, 2H, J = 8.4 Hz), 6.56 (s, 1H), 5.79 (d, 1H, J = 4.4 Hz), 4.97 (d, 1H, J = 4.4 Hz), 4.88 (d, 1H, J = 14.9 Hz), 4.02 (d, 1H, J = 14.9 Hz), 3.56 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 169.6, 164.1, 138.0, 133.3, 132.1, 130.7, 130.8, 127.1, 122.3, 122.1, 120.7, 119.9, 109.3, 102.9, 77.5, 54.0, 29.7, 20.0; IR ($CHCl_3$, cm^{-1}): ν 2929, 1741, 1226, 730; HRMS (ES): calcd for $C_{21}H_{19}BrN_2O_3$ $[M]^+$: 426.0579; found: 426.0560.

Acetoxy β-Lactam ***1e.*** From 846 mg (3.95 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **1e** (740 mg, 60%) as a colorless solid; mp 112−113 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.64 (d, 1H, J = 7.9 Hz), 7.35 (d, 1H, J = 7.9 Hz), 7.27 (td, 1H, J = 7.4, 1.2 Hz), 7.15 (td, 1H, J = 7.4, 1.1 Hz), 6.55 (s, 1H), 5.87 (d, 1H, J = 4.4 Hz), 5.23 (d, 1H, J = 4.4 Hz), 3.73 (s, 3H), 3.43 (dd, 1H, J = 14.0, 8.5 Hz), 2.92 (dd, 1H, J = 14.0, 5.9 Hz), 1.93 (m, 1H), 1.93 (s, 3H), 0.98 (d, 3H, J = 6.7 Hz), 0.95 (d, 3H, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 169.7, 164.7, 138.0, 131.1, 127.0, 122.0, 120.7, 119.8, 109.2, 102.8, 77.4, 55.4, 47.8, 29.8, 27.1,

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20.3, 20.2, 20.0; IR ($CHCl_3$, cm^{-1}): ν 2923, 1742, 1211, 704; HRMS (ES): calcd for $C_{18}H_{22}N_2O_3$ $[M]^+$: 314.1630; found: 314.1641.

Acetoxy β-Lactam ***1f***. From 1.3 g (5.7 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave compound **1f** (592 mg, 45%) as a colorless solid; mp 138−139 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.55 (d, 1H, J = 7.9 Hz), 7.37 (m, 3H), 7.27 (m, 3H), 7.13 (m, 2H), 6.54 (s, 1H), 6.03 (d, 1H, J = 4.8 Hz), 5.63 (d, 1H, J = 4.8 Hz), 3.79 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 169.6, 161.5, 138.2, 136.5, 130.3, 129.2 (2C), 127.1, 124.9, 122.1, 120.8, 119.8, 117.5 (2C), 109.2, 103.7, 76.4, 55.3, 30.1, 20.0; IR ($CHCl_3$, cm^{-1}): ν 2923, 1744, 1215, 730, 699; HRMS (ES): calcd for $C_{20}H_{18}N_2O_3$ $[M]^+$: 334.1317; found: 334.1325.

Transesterification of Acetate Derivatives 1. General Procedure for the Preparation of Hydroxy-β-Lactams 2. Sodium methoxide (102 mg, 1.89 mmol) was added in portions at 0 °C to a solution of the appropriate acetate derivative **1** (1.89 mmol) in methanol (18 mL). The reaction was stirred at 0 °C until disappearance of the starting material (TLC), and then water was added (3 mL). The methanol was removed under reduced pressure, the aqueous residue was extracted with ethyl acetate, and the organic layer was dried ($MgSO_4$). The solvent was removed under reduced pressure, to give analytically pure hydroxy-β-lactams **2**.

Hydroxy β-Lactam ***2a***. From 685 mg (2.0 mmol) of the acetoxy β-lactam **1a**, compound **2a** (479 mg, 80%) was obtained as a colorless solid; mp 129−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.64 (d, 1H, J = 7.8 Hz), 7.33 (m, 5H), 7.18 (m, 3H), 6.55 (s, 1H), 5.07 (br s, 1H), 5.00 (d, 1H, J = 14.8 Hz), 4.92 (d, 1H, J = 4.8 Hz), 4.12 (d, 1H, J = 14.8 Hz), 3.62 (s, 3H), 2.47 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 168.0, 134.7 (2C), 132.9, 129.0 (2C), 128.6 (2C), 128.1, 127.2, 122.4, 120.7, 120.2, 109.2, 101.7, 78.5, 55.5, 44.2, 30.0; IR ($CHCl_3$, cm^{-1}): ν 3102, 2925, 1670, 1612, 750, 701; HRMS (ES): calcd for $C_{19}H_{18}N_2O_2$ $[M]^+$: 306.1368; found: 306.1364.

Hydroxy β-Lactam ***2b***. From 800 mg (2.11 mmol) of the acetoxy β-lactam **1b**, compound **2b** (685 mg, 96%) was obtained as a colorless solid; mp 139−140 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.63 (d, 1H, J = 7.8 Hz), 7.29 (m, 2H), 7.17 (m, 1H), 7.12 (d, 2H, J = 8.3 Hz), 6.85 (d, 2H, J = 8.2 Hz), 6.55 (s, 1H), 5.05 (d, 1H, J = 4.2 Hz), 4.92 (m, 1H), 4.88 (m, 1H), 4.06 (d, 1H, J = 14.7 Hz), 3.80 (s, 1H), 3.62 (s, 3H), 2.78 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 168.1, 159.4, 138.5, 133.0, 129.9 (2C), 127.2, 126.7, 122.0, 120.7, 120.0, 114.3 (2C), 109.1, 101.7, 78.3, 55.3 (2C), 43.6, 30.0; IR ($CHCl_3$, cm^{-1}): ν 3100, 2924, 1650, 1610, 730; HRMS (ES): calcd for $C_{20}H_{20}N_2O_3$ $[M]^+$: 336.1474; found: 336.1460.

Hydroxy β-Lactam ***2c***. From 940 mg (2.57 mmol) of the acetoxy β-lactam **1c**, compound **2c** (790 mg, 95%) was obtained as a colorless solid; mp 138−139 °C; ^{1}H NMR (300 MHz, DMSO, 25 °C) δ: 7.43 (d, 1H, J = 8.2 Hz), 7.35 (d, 2H, J = 9.0 Hz), 7.12 (t, 1H, J = 7.3 Hz), 6.98 (t, 1H, J = 7.0 Hz), 6.92 (d, 2H, J = 8.9 Hz), 6.13 (s, 1H), 5.68 (d, 1H, J = 4.9 Hz), 5.30 (m, 1H), 3.75 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (75 MHz, DMSO, 25 °C) δ: 165.9, 155.7, 137.7, 134.7, 130.7, 126.9, 120.9, 119.8, 119.0, 118.4 (2C), 114.4 (2C), 109.3, 100.9, 77.1, 56.4, 55.2, 30.0; IR ($CHCl_3$, cm^{-1}): ν 3101, 2924, 1667, 1615, 743; HRMS (ES): calcd for $C_{19}H_{18}N_2O_3$ $[M]^+$: 322.1317; found: 322.1326.

Hydroxy β-Lactam ***2d***. From 1.32 g (3.09 mmol) of the acetoxy β-lactam **1d**, compound **2d** (1.19 g, 99%) was obtained as a colorless solid; mp 133−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.63 (d, 1H, J = 7.8 Hz), 7.46 (d, 2H, J = 8.4 Hz), 7.33 (d, 1H, J = 7.9 Hz), 7.27 (td, 1H, J = 7.6, 1.2 Hz), 7.16 (td, 1H, J = 7.3, 1.3 Hz), 7.08 (d, 2H, J = 8.4 Hz), 6.52 (s, 1H), 5.06 (br s, 1H), 4.90 (d, 1H, J = 14.7 Hz), 4.89 (d, 1H, J = 5.0 Hz), 4.08 (d, 1H, J = 14.9 Hz), 3.62 (s, 3H), 3.00 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 166.3, 138.5, 133.6, 132.6, 132.1 (2C), 130.2 (2C), 127.1, 122.3, 122.2, 120.7, 120.1, 109.2, 101.7, 78.4, 55.6, 43.6, 30.0; IR ($CHCl_3$, cm^{-1}): ν 3100, 2930, 1669, 1617, 723; HRMS (ES): calcd for $C_{19}H_{17}BrN_2O_2$ $[M]^+$: 384.0473; found: 384.0487.

Hydroxy β-Lactam ***2e***. From 678 mg (2.16 mmol) of the acetoxy β-lactam **1e**, compound **2e** (588 mg, 94%) was obtained as a colorless solid; mp 125−126 °C; ^{1}H NMR (300 MHz, DMSO, 25 °C) δ: 7.50 (d, 1H, J = 7.7 Hz), 7.42 (d, 1H, J = 8.1 Hz), 7.12 (td, 1H, J = 7.6, 1.2 Hz), 7.01 (td, 1H, J = 7.4, 0.9 Hz), 6.34 (s, 1H), 6.09 (m, 1H), 5.15 (m, 1H), 3.68 (s, 3H), 3.27 (dd, 1H, J = 13.8, 8.6 Hz), 2.90 (dd, 1H, J = 13.8, 5.7 Hz), 1.86 (m, 1H), 0.88 (d, 3H, J = 6.7 Hz), 0.87 (d, 3H, J = 6.7 Hz); ^{13}C NMR (75 MHz, DMSO, 25 °C) δ: 168.9, 137.7, 135.8, 127.1, 120.8, 119.8, 118.9, 109.3, 100.3, 77.8, 56.7, 47.3, 29.8, 26.7, 20.2, 20.1; IR ($CHCl_3$, cm^{-1}): ν 3099, 2925, 1672, 1610, 690; HRMS (ES): calcd for $C_{16}H_{20}N_2O_2$ $[M]^+$: 272.1525; found: 272.1528.

Hydroxy β-Lactam ***2f***. From 595 mg (1.78 mmol) of the acetoxy β-lactam **1f**, compound **2f** (446 mg, 86%) was obtained as a colorless solid; mp 132−133 °C; ^{1}H NMR (300 MHz, DMSO, 25 °C) δ: 7.42 (m, 3H), 7.34 (m, 3H), 7.11 (m, 2H), 6.98 (t, 1H, J = 7.5 Hz), 6.43 (d, 1H, J = 7.6 Hz), 6.13 (s, 1H), 5.73 (d, 1H, J = 5.1 Hz), 5.33 (dd, 1H, J = 7.6, 5.1 Hz), 3.77 (s, 3H); ^{13}C NMR (75 MHz, DMSO, 25 °C) δ: 166.7, 137.8, 137.3, 134.6, 129.2 (2C), 127.0, 123.9, 120.9, 119.9, 119.0, 117.2 (2C), 109.3, 100.8, 77.1, 56.3, 30.0; IR ($CHCl_3$, cm^{-1}): ν 3102, 2923, 1670, 1613, 752, 698; HRMS (ES): calcd for $C_{18}H_{16}N_2O_2$ $[M]^+$: 292.1212; found: 292.1221.

Base-Promoted Reaction between Propargyl Bromide and Hydroxy-β-Lactams 2. General Procedure for the Synthesis of Propargylic Ethers 3a−f. Tetrabutyl ammonium iodide (31.9 mg, 0.086 mmol), 50% aqueous sodium hydroxide (100 mL), and propargyl bromide (13.82 mmol) were sequentially added at room temperature to a solution of the appropriate hydroxy-β-lactam **3** (8.64 mmol) in dichloromethane (100 mL). The reaction was stirred for 20 h, and then water was added (50 mL), before being partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (3 × 50 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/hexanes mixtures as eluent gave analytically pure compounds **3**.

Alkynyl β-Lactam ***3a***. From 470 mg (1.55 mmol) of hydroxy-β-lactam **2a**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **3a** (421 mg, 79%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.63 (d, 1H, J = 7.9 Hz), 7.31 (m, 4H), 7.26 (m, 1H), 7.17 (m, 3H), 6.59 (s, 1H), 5.19 (d, 1H, J = 4.5 Hz), 4.95 (d, 1H, J = 14.6 Hz), 4.88 (d, 1H, J = 4.7 Hz), 4.25 (dd, 1H, J = 16.1, 2.5 Hz), 4.05 (d, 1H, J = 15.0 Hz), 4.00 (dd, 1H, J = 16.1, 2.3 Hz), 3.62 (s, 3H), 2.40 (t, 1H, J = 2.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 166.3, 138.4, 134.6, 132.3, 128.9 (2C), 128.6 (2C), 128.0, 127.4, 122.0, 120.7, 119.8, 109.1, 103.2, 82.4, 78.2, 75.9, 57.8, 54.4, 44.3, 30.3; IR ($CHCl_3$, cm^{-1}): ν 2926, 1753, 1615, 1395, 752, 701; HRMS (ES): calcd for $C_{22}H_{20}N_2O_2$ $[M]^+$: 344.1525; found: 344.1515.

Alkynyl β-Lactam ***3b***. From 403 mg (1.20 mmol) of hydroxy-β-lactam **2b**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **3b** (403 mg, 90%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.63 (d, 1H, J = 7.9 Hz), 7.28 (m, 2H), 7.14 (t, 1H, J = 7.9 Hz), 7.09 (d, 2H, J = 8.6 Hz), 6.83 (d, 2H, J = 8.6 Hz), 6.58 (s, 1H), 5.17 (d, 1H, J = 4.7 Hz), 4.87 (m, 1H), 4.85 (m, 1H), 4.24 (dd, 1H, J = 16.1, 2.3 Hz), 4.00 (d, 1H, J = 14.8 Hz), 3.98 (d, 1H, J = 16.1 Hz), 3.80 (s, 3H), 3.62 (s, 3H), 2.39 (t, 1H, J = 2.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 166.2, 159.4, 138.3, 132.4, 130.0 (2C), 127.4, 126.6, 121.9, 120.7, 119.7, 114.2 (2C), 109.1, 103.2, 82.3, 78.2, 75.8, 57.7, 55.3, 54.2, 43.7, 30.3; IR ($CHCl_3$, cm^{-1}): ν 2924, 1760, 1624, 1245, 734; HRMS (ES): calcd for $C_{23}H_{22}N_2O_3$ $[M]^+$: 374.1630; found: 374.1641.

Alkynyl β-Lactam ***3c***. From 745 mg (2.31 mmol) of hydroxy-β-lactam **2c**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **3c** (367 mg, 44%) as a colorless solid; mp 154−155 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.57 (d, 1H, J = 7.9 Hz), 7.36 (d, 2H, J = 9.0 Hz), 7.34 (m, 1H), 7.25 (t, 1H, J = 7.5 Hz), 7.12 (t, 1H, J = 7.4 Hz), 6.81 (d, 2H, J = 9.1 Hz), 6.56 (s, 1H), 5.51 (d, 1H, J = 5.0 Hz), 5.35 (d, 1H, J = 5.0 Hz), 4.31 (dd, 1H, J = 16.1, 2.4 Hz), 4.08 (dd, 1H, J = 16.1, 2.4 Hz), 3.79 (s, 3H), 3.76 (s, 3H), 2.47 (t, 1H, J = 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 163.3, 156.5, 138.6, 131.8, 130.6, 127.2, 122.0, 120.7, 119.7, 118.7 (2C), 114.4 (2C), 109.1, 103.9, 81.4, 78.1, 76.1, 57.9, 56.1, 55.5, 30.7; IR ($CHCl_3$, cm^{-1}): ν 2920, 1757, 1614, 1360, 746; HRMS (ES): calcd for $C_{22}H_{20}N_2O_3$ $[M]^+$: 360.1474; found: 360.1458.

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Alkynyl β-Lactam ***3d***. From 1.3 g (3.37 mmol) of hydroxy-β-lactam **2d**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **3d** (970 mg, 68%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.63 (d, 1H, *J* = 7.8 Hz), 7.45 (d, 2H, *J* = 8.4 Hz), 7.33 (d, 1H, *J* = 7.8 Hz), 7.26 (td, 1H, *J* = 7.0, 1.2 Hz), 7.15 (td, 1H, *J* = 7.3, 1.2 Hz), 7.06 (d, 2H, *J* = 8.4 Hz), 6.56 (s, 1H), 5.20 (d, 1H, *J* = 4.7 Hz), 4.87 (d, 1H, *J* = 14.8 Hz), 4.87 (d, 1H, *J* = 4.7 Hz), 4.25 (dd, 1H, *J* = 16.1, 2.4 Hz), 4.02 (d, 1H, *J* = 14.9 Hz), 4.00 (dd, 1H, *J* = 16.1, 2.4 Hz), 3.64 (s, 3H), 2.41 (t, 1H, *J* = 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 166.3, 138.3, 133.6 (2C), 132.0 (2C), 130.3 (2C), 127.2, 122.1, 122.0, 120.7, 119.8, 109.1, 103.2, 82.4, 78.0, 76.0, 57.8, 54.5, 43.6, 30.3; IR ($CHCl_3$, cm^{-1}): ν 2920, 1753, 1640, 1390, 735; HRMS (ES): calcd for $C_{22}H_{19}BrN_2O_2$ $[M]^+$: 422.0630; found: 422.0641.

Alkynyl β-Lactam ***3e***. From 530 mg (1.95 mmol) of hydroxy-β-lactam **2e**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **3e** (552 mg, 91%) as a colorless solid; mp 98−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.61 (d, 1H, *J* = 7.8 Hz), 7.35 (d, 1H, *J* = 8.2 Hz), 7.26 (td, 1H, *J* = 7.4, 1.2 Hz), 7.17 (td, 1H, *J* = 7.4, 1.1 Hz), 6.55 (s, 1H), 5.26 (d, 1H, *J* = 4.6 Hz), 5.11 (d, 1H, *J* = 4.6 Hz), 4.25 (dd, 1H, *J* = 16.1, 2.4 Hz), 4.00 (dd, 1H, *J* = 16.1, 2.4 Hz), 3.77 (s, 3H), 3.42 (dd, 1H, *J* = 13.9, 8.5 Hz), 2.87 (dd, 1H, *J* = 13.9, 5.8 Hz), 2.42 (t, 1H, *J* = 2.4 Hz), 1.90 (m, 1H), 0.94 (d, 3H, *J* = 6.5 Hz), 0.92 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 167.0, 138.4, 132.5, 127.2, 122.0, 120.7, 119.8, 109.1, 103.3, 82.1, 78.2, 75.8, 57.7, 56.0, 47.8, 30.5, 27.1, 20.3, 20.2; IR ($CHCl_3$, cm^{-1}): ν 2930, 1763, 1640, 1390, 690; HRMS (ES): calcd for $C_{19}H_{22}N_2O_2$ $[M]^+$: 310.1681; found: 310.1681.

Alkynyl β-Lactam ***3f***. From 424 mg (1.45 mmol) of hydroxy-β-lactam **2f**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **3f** (172 mg, 36%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.58 (d, 1H, *J* = 7.9 Hz), 7.43 (d, 2H, *J* = 7.6 Hz), 7.30 (m, 4H), 7.11 (t, 2H, *J* = 7.3 Hz), 6.57 (s, 1H), 5.55 (d, 1H, *J* = 5.1 Hz), 5.37 (d, 1H, *J* = 5.1 Hz), 4.32 (dd, 1H, *J* = 16.1, 2.3 Hz), 4.08 (dd, 1H, *J* = 16.1, 2.4 Hz), 3.76 (s, 3H), 2.48 (t, 1H, *J* = 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 163.9, 138.5, 137.0, 131.6, 129.2 (2C), 127.2, 124.7, 122.0, 120.7, 119.7, 117.4 (2C), 109.1, 103.8, 81.3, 78.0, 76.2, 57.9, 56.0, 30.7; IR ($CHCl_3$, cm^{-1}): ν 2934, 1750, 1614, 1425, 750, 703; HRMS (ES): calcd for $C_{21}H_{18}N_2O_2$ $[M]^+$: 330.1368; found: 330.1363.

Staudinger Reaction. General Procedure for the Preparation of Alkynyl β-Lactam-Tethered Indoles 4a−f. To a solution of the corresponding imine (10.4 mmol) in dichloromethane (35 mL) and triethylamine (4.2 mL, 30 mmol) was slowly added methoxyacetyl chloride (13 mmol) dissolved in dichloromethane (35 mL) at room temperature under an argon atmosphere. Stirring was continued for 2 h at 80 °C. The reaction was allowed to warm to room temperature, and then, 15 mL of $NaHCO_3$ (aq. sat.) was added before being partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (3 × 50 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using an ethyl acetate/hexanes mixture gave analytically pure compounds **4**.

Alkynyl β-Lactam ***4a***. From 632 mg (3.22 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **4a** (641 mg, 74%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.62 (dd, 1H, *J* = 7.8, 0.9 Hz), 7.36 (dd, 1H, *J* = 8.3, 0.8 Hz), 7.26 (td, 1H, *J* = 8.3, 1.2 Hz), 7.14 (td, 1H, *J* = 7.4, 1.1 Hz), 6.58 (s, 1H), 5.19 (d, 1H, *J* = 4.7 Hz), 4.87 (d, 1H, *J* = 4.7 Hz), 4.47 (dd, 1H, *J* = 17.7, 2.6 Hz), 3.82 (dd, 1H, *J* = 17.6, 2.5 Hz), 3.82 (s, 3H), 3.31 (s, 3H), 2.25 (t, 1H, *J* = 2.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 166.1, 138.4, 132.3, 127.3, 122.0, 120.7, 119.8, 109.1, 103.0, 86.1, 75.9, 73.0, 58.5, 54.9, 30.4, 29.7; IR ($CHCl_3$, cm^{-1}): ν 2920, 1750, 1618, 1246, 1243; HRMS (ES): calcd for $C_{16}H_{16}N_2O_2$ $[M]^+$: 268.1212; found: 268.1224.

Alkynyl β-Lactam ***4b***. From 678 mg (2.94 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **4b** (689 mg, 77%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.56 (d, 1H, *J* = 1.5 Hz), 7.26 (d, 1H, *J* = 8.9 Hz), 7.19 (dd, 1H, *J* = 8.8, 2.0 Hz), 6.51 (s, 1H), 5.15 (d, 1H, *J* = 4.8 Hz), 4.87 (d, 1H, *J* = 4.7 Hz), 4.45 (dd, 1H, *J* = 17.7, 2.5 Hz), 3.82 (dd, 1H, *J* = 17.7, 2.5 Hz), 3.77 (s, 3H), 3.31 (s, 3H), 2.25 (t, 1H, *J* = 2.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 166.0, 136.7, 133.9, 128.2, 125.5, 122.3, 120.0, 110.1, 102.5, 86.1, 75.8, 73.2, 58.6, 54.8, 30.6, 29.8; IR ($CHCl_3$, cm^{-1}): ν 2926, 1751, 1620, 1256, 1237; HRMS (ES): calcd for $C_{16}H_{15}ClN_2O_2$ $[M]^+$: 302.0822; found: 302.0825.

Alkynyl β-Lactam ***4c***. From 324 mg (1.43 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **4c** (271 mg, 71%) as a colorless solid; mp 160−161 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.24 (d, 1H, *J* = 8.9 Hz), 7.07 (d, 1H, *J* = 2.5 Hz), 6.91 (dd, 1H, *J* = 8.9, 2.5 Hz), 6.49 (s, 1H), 5.15 (d, 1H, *J* = 4.6 Hz), 4.86 (d, 1H, *J* = 4.6 Hz), 4.45 (dd, 1H, *J* = 17.7, 2.5 Hz), 3.86 (s, 3H), 3.80 (dd, 1H, *J* = 17.7, 2.5 Hz), 3.76 (s, 3H), 3.30 (s, 3H), 2.25 (t, 1H, *J* = 2.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 166.1, 154.3, 133.7, 132.7, 127.6, 112.4, 109.8, 102.5, 102.3, 86.1, 75.9, 73.0, 58.5, 55.9, 54.8, 30.5, 29.7; IR ($CHCl_3$, cm^{-1}): ν 2932, 1756, 1635, 1260, 1248; HRMS (ES): calcd for $C_{17}H_{18}N_2O_3$ $[M]^+$: 298.1317; found: 298.1317.

Alkynyl β-Lactam ***4d***. From 884 mg (4.17 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **4d** (696 mg, 59%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.81 (d, 1H, *J* = 7.8 Hz), 7.35 (d, 1H, *J* = 8.2 Hz), 7.25 (td, 1H, *J* = 7.6, 1.2 Hz), 7.13 (td, 1H, *J* = 7.4, 1.1 Hz), 6.56 (s, 1H), 5.24 (d, 1H, *J* = 4.6 Hz), 4.89 (d, 1H, *J* = 4.6 Hz), 3.80 (m, 1H), 3.78 (s, 3H), 3.29 (s, 3H), 3.23 (m, 1H), 2.47 (m, 2H), 2.01 (t, 1H, *J* = 2.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 167.0, 138.4, 132.7, 127.3, 122.0, 120.7, 119.8, 109.1, 103.1, 86.0, 80.7, 70.5, 58.5, 56.1, 38.8, 30.5, 17.8; IR ($CHCl_3$, cm^{-1}): ν 2920, 1747, 1630, 1259, 1230; HRMS (ES): calcd for $C_{17}H_{18}N_2O_2$ $[M]^+$: 282.1368; found: 282.1376.

Alkynyl β-Lactam ***4e***. From 700 mg (2.86 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **4e** (589 mg, 65%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.54 (d, 1H, *J* = 1.9 Hz), 7.24 (d, 1H, *J* = 8.8 Hz), 7.17 (dd, 1H, *J* = 8.8, 2.0 Hz), 6.48 (s, 1H), 5.21 (d, 1H, *J* = 4.6 Hz), 4.87 (d, 1H, *J* = 4.6 Hz), 3.77 (m, 1H), 3.75 (s, 3H), 3.28 (s, 3H), 3.22 (m, 1H), 2.48 (m, 2H), 2.01 (t, 1H, *J* = 2.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 166.8, 136.7, 134.3, 128.1, 125.4, 122.1, 119.9, 110.1, 102.4, 85.9, 80.6, 70.5, 58.5, 55.9, 38.9, 30.6, 17.8; IR ($CHCl_3$, cm^{-1}): ν 2932, 1754, 1610, 1390, 1215; HRMS (ES): calcd for $C_{17}H_{17}ClN_2O_2$ $[M]^+$: 316.0979; found: 316.0969.

Alkynyl β-Lactam ***4f***. From 406 mg (1.69 mmol) of the appropriate imine, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **4f** (247 mg, 47%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.23 (d, 1H, *J* = 8.9 Hz), 7.06 (d, 1H, *J* = 2.4 Hz), 6.91 (dd, 1H, *J* = 8.9, 2.5 Hz), 6.47 (s, 1H), 5.19 (d, 1H, *J* = 4.6 Hz), 4.87 (d, 1H, *J* = 4.6 Hz), 3.85 (s, 3H), 3.79 (m, 1H), 3.74 (s, 3H), 3.28 (s, 3H), 3.25 (m, 1H), 2.48 (m, 2H), 2.01 (t, 1H, *J* = 2.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 167.0, 154.2, 133.8, 133.1, 127.5, 122.4, 109.8, 102.6, 102.2, 86.0, 80.7, 70.5, 58.5, 56.0, 55.8, 38.8, 30.9, 17.8; IR ($CHCl_3$, cm^{-1}): ν 2926, 1758, 1623, 1298, 1234; HRMS (ES): calcd for $C_{18}H_{20}N_2O_3$ $[M]^+$: 312.1474; found: 312.1470.

Cu-Catalyzed Reaction of β-Lactam-Tethered Alkynyl Indoles 3 and 4. General Procedure for the Preparation of β-Lactam-Tethered Allenyl Indoles 5a−f and 6a−f. A well stirred solution of $(CH_2O)_n$ (0.5 mmol), CuI (0.1 mmol), the appropriate alkyne **3** or **4** (0.2 mmol), and *N*,*N*-diisopropylethylamine (Hüning's base) (0.36 mmol) in dioxane (1 mL) was refluxed under an argon atmosphere. When the reaction was complete, as monitored by TLC, it was cooled to rt. Water (5 mL) was added before being extracted with ethyl acetate (3 × 15 mL). The organic phase was washed with water (2 × 5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds **5** or **6**. Spectroscopic and analytical data for previously allenes **5** or **6** follow.

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Allenyl β-Lactam ***5a***. From 406 mg (1.20 mmol) of alkynyl-β-lactam **3a**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **5a** (266 mg, 63%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.62 (d, 1H, *J* = 7.8 Hz), 7.28 (m, 5H), 7.15 (m, 3H), 6.59 (s, 1H), 4.98 (d, 1H, *J* = 4.5 Hz), 4.92 (d, 1H, *J* = 14.9 Hz), 4.91 (m, 1H), 4.83 (d, 1H, *J* = 4.4 Hz), 4.64 (m, 2H), 4.01 (d, 1H, *J* = 14.7 Hz), 3.96 (t, 1H, *J* = 2.3 Hz), 3.94 (t, 1H, *J* = 2.3 Hz), 3.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 209.6, 166.7, 138.4, 134.7, 132.4, 128.9 (2C), 128.7 (2C), 128.0, 127.4, 121.9, 120.7, 119.7, 109.1, 103.6, 86.7, 83.5, 75.8, 68.7, 55.0, 44.2, 30.4; IR ($CHCl_3$, cm^{-1}): ν 2953, 1756, 1616, 1397, 751, 701; HRMS (ES): calcd for $C_{23}H_{22}N_2O_2$ $[M]^+$: 358.1681; found: 358.1693.

Allenyl β-Lactam ***5b***. From 434 mg (1.16 mmol) of alkynyl-β-lactam **3b**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound **5b** (353 mg, 78%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.62 (d, 1H, *J* = 7.7 Hz), 7.32 (d, 1H, *J* = 8.0 Hz), 7.25 (td, 1H, *J* = 8.1, 1.2 Hz), 7.14 (td, 1H, *J* = 7.9, 1,2 Hz), 7.08 (d, 2H, *J* = 8.6 Hz), 6.82 (d, 2H, *J* = 8.6 Hz), 6.58 (s, 1H), 4.96 (d, 1H, *J* = 4.5 Hz), 4.92 (t, 1H, *J* = 6.9 Hz), 4.85 (d, 1H, *J* = 14.5 Hz), 4.80 (d, 1H, *J* = 4.5 Hz), 4.63 (m, 2H), 3.96 (d, 1H, *J* = 14.9 Hz), 3.94 (m, 2H), 3.79 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 209.6, 166.5, 159.3, 138.4, 132.6, 130.0 (2C), 127.4, 126.7, 121.9, 120.7, 119.7, 114.2 (2C), 109.1, 103.6, 86.7, 83.5, 75.7, 68.7, 55.3, 54.8, 43.7, 30.4; IR ($CHCl_3$, cm^{-1}): ν 2950, 1752, 1615, 1398, 734; HRMS (ES): calcd for $C_{24}H_{24}N_2O_3$ $[M]^+$: 388.1787; found: 388.1784.

Allenyl β-Lactam ***5c***. From 262 mg (0.73 mmol) of alkynyl-β-lactam **3c**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **5c** (165 mg, 60%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.49 (d, 1H, *J* = 7.9 Hz), 7.27 (d, 2H, *J* = 9.0 Hz), 7.25 (d, 1H, *J* = 8.2 Hz), 7.16 (td, 1H, *J* = 8.3, 1,2 Hz), 7.03 (td, 1H, *J* = 7.9, 1.0 Hz), 6.71 (d, 2H, *J* = 9.1 Hz), 6.49 (s, 1H), 5.38 (d, 1H, *J* = 4.8 Hz), 5.06 (d, 1H, *J* = 4.8 Hz), 4.90 (q, 1H, *J* = 6.9 Hz), 4.57 (m, 2H), 3.94 (dd, 2H, *J* = 6.8, 1.2 Hz), 3.70 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 209.7, 163.7, 156.5, 138.7, 132.0, 130.7, 127.3, 122.0, 120.7, 119.7, 118.7, 114.4 (2C), 109.1, 104.2, 86.7, 82.7, 75.8, 68.8, 56.8, 55.4, 30.9; IR ($CHCl_3$, cm^{-1}): ν 2945, 1759, 1618, 1387, 735; HRMS (ES): calcd for $C_{23}H_{22}N_2O_3$ $[M]^+$: 374.1630; found: 374.1616.

Allenyl β-Lactam ***5d***. From 489 mg (1.55 mmol) of alkynyl-β-lactam **3d**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **5d** (339 mg, 50%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.63 (d, 1H, *J* = 7.7 Hz), 7.44 (d, 2H, *J* = 8.3 Hz), 7.33 (d, 1H, *J* = 8.2 Hz), 7.26 (td, 1H, *J* = 6.9, 1.2 Hz), 7.14 (t, 1H, *J* = 7.9 Hz), 7.05 (d, 2H, *J* = 8.5 Hz), 6.57 (s, 1H), 4.99 (d, 1H, *J* = 4.5 Hz), 4.92 (qu, 1H, *J* = 7.0 Hz), 4.85 (d, 1H, *J* = 12.7 Hz), 4.82 (d, 1H, *J* = 4.4 Hz), 4.65 (m, 2H), 3.99 (d, 1H, *J* = 12.2 Hz), 3.96 (m, 2H), 3.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 209.6, 166.6, 138.4, 133.7, 132.1, 132.0 (2C), 130.3 (2C), 127.3, 122.1, 122.0, 120.7, 119.8, 109.1, 103.6, 86.6, 83.5, 75.8, 68.8, 55.0, 43.6, 30.5; IR ($CHCl_3$, cm^{-1}): ν 2952, 1758, 1620, 1297, 754; HRMS (ES): calcd for $C_{23}H_{21}BrN_2O_2$ $[M]^+$: 436.0786; found: 436.0799.

Allenyl β-Lactam ***5e***. From 524 mg (1.69 mmol) of alkynyl-β-lactam **3e**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **5e** (443 mg, 81%) as a colorless solid; mp 98−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.61 (d, 1H, *J* = 7.7 Hz), 7.35 (d, 1H, *J* = 8.2 Hz), 7.25 (td, 1H, *J* = 7.4, 1.2 Hz), 7.13 (td, 1H, *J* = 7.3, 1.2 Hz), 6.56 (s, 1H), 5.07 (m, 1H), 5.05 (m, 1H), 4.94 (q, 1H, *J* = 6.7 Hz), 4.65 (m, 2H), 3.96 (m, 2H), 3.78 (s, 3H), 3.89 (dd, 1H, *J* = 13.9, 8.5 Hz), 2.83 (dd, 1H, *J* = 13.9, 5.9 Hz), 1.89 (m, 1H), 0.93 (d, 3H, *J* = 6.6 Hz), 0.91 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 209.5, 167.3, 138.4, 132.6, 127.3, 121.9, 120.6, 119.7, 109.1, 103.7, 86.7, 83.3, 75.7, 68.7, 56.6, 47.8, 30.6, 27.1, 20. 4, 20.3; IR ($CHCl_3$, cm^{-1}): ν 2953, 1759, 1614, 1395, 741; HRMS (ES): calcd for $C_{20}H_{24}N_2O_2$ $[M]^+$: 324.1838; found: 324.1845.

Allenyl β-Lactam ***5f***. From 68 mg (0.21 mmol) of alkynyl-β-lactam **3f**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **5f** (30 mg, 42%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.59 (d, 1H, *J* = 7.8 Hz), 7.43 (d, 2H, *J* = 8.5 Hz), 7.28 (m, 4H), 7.14 (d, 1H, *J* = 7.9 Hz), 7.10 (t, 1H, *J* = 7.4 Hz), 6.60 (s, 1H), 5.52 (d, 1H, *J* = 4.9 Hz), 5.17 (d, 1H, *J* = 5.0 Hz), 5.00 (q, 1H, *J* = 6.9 Hz), 4.67 (m, 2H), 4.04 (dt, 2H, *J* = 7.2, 2.2 Hz), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 209.7, 164.3, 138.7, 137.1, 131.9, 129.2 (2C), 127.2, 124.6, 122.0, 120.7), 119.7, 117.3 (2C), 109.1, 104.1, 86.6, 82.6, 75.8, 68.9, 56.6, 30.9; IR ($CHCl_3$, cm^{-1}): ν 2955, 1755, 1619, 1395, 752, 700; HRMS (ES): calcd for $C_{22}H_{20}N_2O_2$ $[M]^+$: 344.1525; found: 344.1519.

Allenyl β-Lactam ***6a***. From 292 mg (1.1 mmol) of alkynyl-β-lactam **4a**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **6a** (236 mg, 77%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.61 (d, 1H, *J* = 7.9 Hz), 7.35 (d, 1H, *J* = 8.0 Hz), 7.25 (td, 1H, *J* = 8.2, 1.0 Hz), 7.13 (td, 1H, *J* = 7.5, 0.9 Hz), 6.57 (s, 1H), 5.12 (d, 1H, *J* = 4.5 Hz), 5.11 (m, 1H), 4.85 (d, 1H, *J* = 4.7 Hz), 4.80 (m, 2H), 4.27 (m, 1H), 3.78 (s, 3H), 3.60 (m, 1H), 3.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 209.2, 166.7, 138.4, 132.8, 127.3, 121.9, 120.7, 119.7, 109.0, 103.1, 85.9, 85.1, 77.4, 58.5, 55.3, 38.6, 30.4; IR ($CHCl_3$, cm^{-1}): ν 2954, 1760, 1616, 1390, 1240; HRMS (ES): calcd for $C_{17}H_{18}N_2O_2$ $[M]^+$: 282.1368; found: 282.1379.

Allenyl β-Lactam ***6b***. From 320 mg (1.06 mmol) of alkynyl-β-lactam **4b**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **6b** (201 mg, 60%) as a colorless solid; mp 105−106 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.56 (d, 1H, *J* = 1.9 Hz), 7.25 (d, 1H, *J* = 8.8 Hz), 7.18 (dd, 1H, *J* = 8.7, 1.9 Hz), 6.50 (s, 1H), 5.10 (m, 1H), 5.09 (d, 1H, *J* = 5.0 Hz), 4.85 (d, 1H, *J* = 4.7 Hz), 4.80 (m, 2H), 4.26 (m, 1H), 3.75 (s, 3H), 3.60 (m, 1H), 3.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 209.2, 166.6, 136.7, 134.3, 128.2, 125.4, 122.1, 120.0, 110.1, 102.5, 85.8, 85.0, 77.9, 58.5, 55.1, 38.7, 30.7; IR ($CHCl_3$, cm^{-1}): ν 2950, 1753, 1624, 1379, 1251; HRMS (ES): calcd for $C_{17}H_{17}ClN_2O_2$ $[M]^+$: 316.0979; found: 316.0977.

Allenyl β-Lactam ***6c***. From 170 mg (0.57 mmol) of alkynyl-β-lactam **4c**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **6c** (84 mg, 47%) as a colorless solid; mp 111−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.23 (d, 1H, *J* = 8.9 Hz), 7.06 (d, 1H, *J* = 2.4 Hz), 6.91 (dd, 1H, *J* = 8.9, 2.5 Hz), 6.48 (s, 1H), 5.10 (m, 1H), 5.09 (d, 1H, *J* = 4.6 Hz), 4.84 (d, 1H, *J* = 4.6 Hz), 4.80 (m, 2H), 4.26 (m, 1H), 3.85 (s, 3H), 3.74 (s, 3H), 3.59 (m, 1H), 3.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 209.2, 166.7, 154.3, 133.8, 133.1, 127.6, 112.3, 109.8, 102.7, 102.3, 85.9, 85.1, 77.4, 58.5, 55.9, 55.2, 38.5, 30.6; IR ($CHCl_3$, cm^{-1}): ν 2950, 1755, 1623, 1387, 1236; HRMS (ES): calcd for $C_{18}H_{20}N_2O_3$ $[M]^+$: 312.1474; found: 312.1474.

Allenyl β-Lactam ***6d***. From 215 mg (0.76 mmol) of alkynyl-β-lactam **4d**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **6d** (104 mg, 46%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.51 (d, 1H, *J* = 7.8 Hz), 7.25 (d, 1H, *J* = 8.2 Hz), 7.15 (td, 1H, *J* = 7.6, 1.2 Hz), 7.03 (td, 1H, *J* = 7.4, 1.1 Hz), 6.46 (s, 1H), 4.98 (d, 1H, *J* = 4.5 Hz), 4.97 (m, 1H), 4.70 (d, 1H, *J* = 4.7 Hz), 4.62 (m, 2H), 3.67 (s, 3H), 3.62 (m, 1H), 3.17 (s, 3H), 3.06 (m, 1H), 2.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 208.7, 166.8, 138.3, 132.8, 127.2, 121.8, 120.5, 119.6, 109.0, 103.0, 86.5, 85.7, 75.7, 58.3, 55.6, 39.5, 30.4, 26.1; IR ($CHCl_3$, cm^{-1}): ν 2960, 1757, 1616, 1387, 1234; HRMS (ES): calcd for $C_{18}H_{20}N_2O_2$ $[M]^+$: 296.1525; found: 296.1525.

Allenyl β-Lactam ***6e***. From 166 mg (0.52 mmol) of alkynyl-β-lactam **4e**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **6e** (95 mg, 55%) as a colorless solid; mp 98−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.56 (d, 1H, *J* = 1.9 Hz), 7.25 (d, 1H, *J* = 8.8 Hz), 7.18 (td, 1H, *J* = 8.7, 2.0 Hz), 6.49 (s, 1H), 5.05 (q, 1H, *J* = 6.7 Hz), 5.04 (d, 1H, *J* = 4.5 Hz), 4.81 (d, 1H, *J* = 4.6 Hz), 4.72 (m, 2H), 3.75 (s, 3H), 3.69 (m, 1H), 3.29 (s, 3H), 3.16 (m, 1H), 2.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 208.8, 166.9, 136.8, 134.4, 128.2, 125.5, 122.2, 120.0, 110.1, 102.6, 86.5, 85.8, 75.9, 58.5, 55.6, 39.7, 30.7, 26.2; IR ($CHCl_3$, cm^{-1}): ν 2950, 1756, 1624, 1385, 1238; HRMS (ES): calcd for $C_{18}H_{19}ClN_2O_2$ $[M]^+$: 330.1135; found: 330.1135.

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Allenyl β-Lactam ***6f***. From 500 mg (1.6 mmol) of alkynyl-β-lactam **4f**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **6f** (261 mg, 50%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.23 (d, 1H, *J* = 8.9 Hz), 7.06 (d, 1H, *J* = 2.3 Hz), 6.90 (dd, 1H, *J* = 8.9, 2.5 Hz), 6.48 (s, 1H), 5.05 (m, 1H), 5.03 (d, 1H, *J* = 4.4 Hz), 4.79 (d, 1H, *J* = 4.5 Hz), 4.72 (m, 2H), 3.90 (s, 3H), 3.73 (s, 3H), 3.68 (m, 1H), 3.20 (s, 3H), 3.15 (m, 1H), 2.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 208.8, 166.9, 154.2, 133.8, 133.2, 127.5, 122.3, 109.8, 102.7, 102.2, 86.5, 85.8, 75.8, 58.4, 55.8, 55.6, 39.6, 30.6, 26.2; IR ($CHCl_3$, cm^{-1}): ν 2950, 1760, 1615, 1394, 1243; HRMS (ES): calcd for $C_{19}H_{22}N_2O_3$ $[M]^+$: 326.1630; found: 326.1630.

General Procedure for the Gold-Catalyzed Hydroarylation Reaction of β-Lactam-Tethered Allenyl Indoles 5. Preparation of Azeto-oxepino[4,5-*b*]indol-2-ones 7. The appropriate allene **5** (1.0 mmol) was added to a stirred solution of [AuClIPr] (0.05 mmol) and $AgSbF_6$ (0.05 mmol) in 1,2-dichloroethane (13.0 mL) under argon. The resulting mixture was stirred at room temperature until disappearance of the starting material (TLC). After filtration through a pad of Celite, the mixture was extracted with ethyl acetate (3 × 5 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate or dichloromethane/ethyl acetate mixtures gave analytically pure tetracyclic compounds **7**.

Tetracycle ***7a***. From 85 mg (0.24 mmol) of allene **5a**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **7a** (61 mg, 72%) as a colorless solid; mp 142−143 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 8.02 (d, 1H, *J* = 8.0 Hz), 7.28 (m, 4H), 7.21 (m, 3H), 7.08 (td, 1H, *J* = 7.3, 1.4 Hz), 5.73 (m, 1H), 5.49 (d, 1H, *J* = 5.0 Hz), 5.32 (d, 1H, *J* = 16.6 Hz), 5.23 (dd, 1H, *J* = 10.0, 1.3 Hz), 5.01 (d, 1H, *J* = 5.0 Hz), 4.90 (d, 1H, *J* = 15.8 Hz), 4.19 (m, 2H), 4.14 (d, 1H, *J* = 15.8 Hz), 3.98 (m, 1H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 167.7, 137.9, 137.4, 135.2, 129.3, 128.9 (2C), 128.0, 127.7, 127.6 (2C), 122.8, 121.1, 119.3, 117.6, 115.1, 109.2, 87.5, 70.5, 54.7, 44.6, 43.9, 29.8; IR ($CHCl_3$, cm^{-1}): ν 2933, 1751, 1132, 927, 743, 700; HRMS (ES): calcd for $C_{23}H_{22}N_2O_2$ $[M]^+$: 358.1681; found: 358.1694.

Tetracycle ***7b***. From 33 mg (0.085 mmol) of allene **5b**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **7b** (23 mg, 68%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.67 (d, 1H, *J* = 8.0 Hz), 7.21 (m, 2H), 7.09 (m, 3H), 6.82 (d, 2H, *J* = 8.6 Hz), 5.73 (m, 1H), 5.46 (d, 1H, *J* = 5.0 Hz), 5.32 (d, 1H, *J* = 17.0 Hz), 5.23 (d, 1H, *J* = 10.1 Hz), 4.99 (d, 1H, *J* = 5.0 Hz), 4.84 (d, 1H, *J* = 15.6 Hz), 4.18 (m, 2H), 4.07 (d, 1H, *J* = 15.6 Hz), 3.97 (m, 1H), 3.77 (s, 3H), 3.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 167.6, 159.3, 137.8, 137.4, 128.9 (2C), 127.8, 127.5, 127.1, 122.7, 121.0, 119.3, 117.5, 115.0, 114.3 (2C), 109.1, 87.4, 70.4, 55.3, 54.5, 44.0, 43.9, 29.8; IR ($CHCl_3$, cm^{-1}): ν 2935, 1750, 1134, 929, 735; HRMS (ES): calcd for $C_{24}H_{24}N_2O_3$ $[M]^+$: 388.1787; found: 388.1764.

Tetracycle ***7c***. From 59 mg (0.16 mmol) of allene **5c**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **7c** (27 mg, 63%) as a colorless solid; mp 109−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.70 (d, 1H, *J* = 7.9 Hz), 7.34 (m, 2H), 7.19 (d, 2H, *J* = 9.1 Hz), 7.14 (m, 1H), 6.82 (d, 2H, *J* = 9.1 Hz), 5.75 (m, 1H), 5.51 (d, 1H, *J* = 5.1 Hz), 5.41 (d, 1H, *J* = 5.1 Hz), 5.27 (d, 1H, *J* = 17.1 Hz), 5.17 (dd, 1H, *J* = 10.1, 1.3 Hz), 4.27 (m, 1H), 4.23 (m, 1H), 4.06 (m, 1H), 3.77 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 165.0, 157.8, 138.0, 137.2, 129.6, 127.9, 127.6, 123.0, 122.1 (2C), 121.0, 119.6, 117.5, 115.5, 114.6 (2C), 109.5, 87.0, 69.9, 57.0, 55.4, 43.6, 30.6; IR ($CHCl_3$, cm^{-1}): ν 2933, 1755, 1129, 929, 738; HRMS (ES): calcd for $C_{23}H_{22}N_2O_3$ $[M]^+$: 374.1630; found: 374.1637.

Tetracycle ***7d***. From 131 mg (0.30 mmol) of allene **5d**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **7d** (107 mg, 82%) as a colorless solid; mp 155−156 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.57 (d, 1H, *J* = 8.0 Hz), 7.33 (d, 2H, *J* = 8.5 Hz), 7.17 (m, 1H), 7.14 (t, 1H, *J* = 7.6 Hz), 6.99 (m, 1H), 6.98 (d, 2H, *J* = 8.2 Hz), 5.63 (m, 1H), 5.39 (d, 1H, *J* = 5.0 Hz), 5.21 (d, 1H, *J* = 16.9 Hz), 5.15 (dd, 1H, *J* = 10.2, 1.5 Hz), 4.91 (d, 1H, *J* = 5.1 Hz), 4.68 (d, 1H, *J* = 15.9 Hz), 4.10 (m, 1H), 4.07 (m, 1H), 4.05 (d, 1H, *J* = 15.8 Hz), 3.85 (m, 1H), 3.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 167.7, 137.8, 137.1, 134.3, 132.0 (2C), 129.2 (2C), 127.4, 127.3, 122.9, 121.9, 121.0, 119.4, 117.7, 115.1, 109.1, 87.5, 70.5, 57.0, 54.8), 44.0, 43.9, 29.9; IR ($CHCl_3$, cm^{-1}): ν 2935, 1753, 1129, 924, 732; HRMS (ES): calcd for $C_{23}H_{21}BrN_2O_2$ $[M]^+$: 436.0786; found: 436.0804.

Tetracycle ***7e***. From 53 mg (0.16 mmol) of allene **5e**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **7e** (47 mg, 89%) as a colorless solid; mp 143−144 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.69 (d, 1H, *J* = 8.1 Hz), 7.29 (m, 2H), 7.10 (td, 1H, *J* = 7.1, 1.9 Hz), 5.73 (m, 1H), 5.43 (d, 1H, *J* = 5.0 Hz), 5.33 (d, 1H, *J* = 16.5 Hz), 5.22 (d, 1H, *J* = 10.1 Hz), 5.05 (d, 1H, *J* = 5.1 Hz), 4.19 (m, 1H), 4.16 (m, 1H), 3.96 (m, 1H), 3.78 (s, 3H), 3.26 (dd, 1H, *J* = 14.1, 8.2 Hz), 3.04 (dd, 1H, *J* = 14.1, 6.4 Hz), 1.70 (m, 1H), 0.87 (d, 3H, *J* = 2.3 Hz), 0.84 (d, 3H, *J* = 2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 167.6, 137.8, 137.2, 128.5, 127.5, 122.8, 121.2, 119.3, 117.7, 114.9, 109.2, 87.2, 70.4, 56.0, 49.7, 44.0, 30.1, 27.8, 20.3, 20.2; IR ($CHCl_3$, cm^{-1}): ν 2935, 1752, 1130, 925, 732; HRMS (ES): calcd for $C_{20}H_{24}N_2O_2$ $[M]^+$: 324.1838; found: 324.1832.

General Procedure for the Gold-Catalyzed Hydroarylation/N1−C4 β-Lactam Cleavage of β-Lactam-Tethered Allenyl Indoles 5. Preparation of 1,6-Dihydro-2*H*-oxepino[4,5-*b*]-indole-4-carboxamides 8. The appropriate allene **5** (1.0 mmol) was added to a stirred solution of [AuClIPr] (0.05 mmol) and $AgSbF_6$ (0.05 mmol) in 1,2-dichloroethane (13.0 mL) under argon. The resulting mixture was stirred at room temperature (**5f**) or at 84 °C (**5a−e**), until disappearance of the starting material (TLC). After filtration through a pad of Celite, the mixture was extracted with ethyl acetate (3 × 5 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure tricyclic compounds **8**.

Tricycle ***8a***. From 85 mg (0.24 mmol) of allene **5a**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **8a** (51 mg, 60%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.52 (d, 1H, *J* = 7.9 Hz), 7.36 (m, 4H), 7.33 (m, 3H), 7.23 (s, 1H), 7.15 (br s, 1H), 7.10 (t, 1H, *J* = 7.9 Hz), 6.02 (m, 1H), 5.15 (d, 1H, *J* = 10.1 Hz), 5.06 (d, 1H, *J* = 17.0 Hz), 4.67 (dd, 1H, *J* = 11.1, 3.3 Hz), 4.57 (m, 2H), 4.19 (m, 1H), 4.04 (dd, 1H, *J* = 11.1, 1.3 Hz), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 162.9, 148.0, 138.1, 137.7, 130.7, 128.7 (2C), 128.1, 127.6 (2C), 127.0, 122.9, 119.7, 118.6, 117.0, 116.8, 109.4, 101.0, 72.9, 43.8, 43.2, 29.6; IR ($CHCl_3$, cm^{-1}): ν 3401, 2925, 1682, 1522, 1361, 755, 700; HRMS (ES): calcd for $C_{23}H_{22}N_2O_2$ $[M]^+$: 358.1681; found: 358.1680.

Tricycle ***8b***. From 40 mg (0.10 mmol) of allene **5b**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **8b** (21 mg, 53%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.55 (d, 1H, *J* = 7.9 Hz), 7.33 (d, 2H, *J* = 8.6 Hz), 7.32 (m, 1H), 7.29 (m, 1H), 7.28 (m, 1H), 7.13 (td, 1H, *J* = 7.4, 1.3 Hz), 7.14 (br s, 1H), 6.93 (d, 2H, *J* = 8.6 Hz), 6.04 (m, 1H), 5.18 (d, 1H, *J* = 10.1 Hz), 5.09 (d, 1H, *J* = 17.0 Hz), 4.69 (dd, 1H, *J* = 11.1, 3.4 Hz), 4.54 (m, 2H), 4.21 (m, 1H), 4.05 (dd, 1H, *J* = 11.1, 1.3 Hz), 3.85 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 162.7, 159.1, 148.1, 137.7, 137.5, 130.6, 130.2, 129.4 (2C), 126.9, 122.8, 119.6, 118.5, 116.8, 116.7, 114.0 (2C), 109.4, 100.9, 72.8, 55.3, 43.2, 43.1, 29.5; IR ($CHCl_3$, cm^{-1}): ν 3400, 2928, 1685, 1528, 1403, 735; HRMS (ES): calcd for $C_{24}H_{24}N_2O_3$ $[M]^+$: 388.1787; found: 388.1798.

Tricycle ***8c***. From 71 mg (0.19 mmol) of allene **5c**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **8c** (48 mg, 67%) as a colorless solid; mp 148−149 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 8.51 (s, 1H), 7.56 (d, 2H, *J* = 9.1 Hz), 7.50 (dt, 1H, *J* = 7.9, 0.9 Hz), 7.26 (m, 2H), 7.22 (m, 1H), 7.07 (td, 1H, *J* = 7.3, 1.3 Hz), 6.87 (d, 2H, *J* = 9.1 Hz), 6.03 (m, 1H), 5.16 (dt, 1H, *J* = 10.0, 1.3 Hz), 5.05 (dt, 1H, *J* = 17.0, 1.4 Hz), 4.75 (dd, 1H, *J* = 11.1, 3.3 Hz), 4.19 (m, 1H), 4.07 (dd, 1H, *J* = 11.1,

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1.4 Hz), 3.78 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 160.4, 156.4, 148.0, 137.7, 137.6, 130.8, 130.6, 126.9, 123.0, 121.4 (2C), 119.7, 118.7, 117.1, 117.0, 114.2 (2C), 109.5, 101.4, 73.0, 55.4, 43.1, 29.5; IR ($CHCl_3$, cm^{-1}): ν 3398, 2920, 1678, 1530, 1354, 736; HRMS (ES): calcd for $C_{23}H_{22}N_2O_3$ $[M]^+$: 374.1630; found: 374.1630.

Tricycle ***8d***. From 72 mg (0.17 mmol) of allene **5d**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **8d** (29 mg, 40%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 8.55 (d, 1H, J = 8.0 Hz), 7.52 (d, 2H, J = 8.5 Hz), 7.34 (t, 1H, J = 8.2 Hz), 7.31 (m, 1H), 7.29 (m, 1H), 7.28 (d, 2H, J = 8.5 Hz), 7.21 (m, 1H), 7.14 (t, 1H, J = 7.3 Hz), 6.04 (m, 1H), 5.20 (dt, 1H, J = 10.1, 1.3 Hz), 5.10 (dt, 1H, J = 17.0, 1.5 Hz), 4.72 (dd, 1H, J = 11.1, 3.4 Hz), 4.60 (dd, 1H, J = 14.9, 6.1 Hz), 4.52 (dd, 1H, J = 14.9, 6.0 Hz), 4.23 (m, 1H), 4.07 (dd, 1H, J = 11.1, 1.3 Hz), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 163.0, 147.7, 137.6, 137.6, 137.2, 131.8 (2C), 130.5, 129.7 (2C), 126.9, 122.9, 121.4, 119.7, 118.6, 117.0, 116.9, 109.4, 101.1, 72.8, 43.1, 43.1, 29.6; IR ($CHCl_3$, cm^{-1}): ν 3390, 2928, 1682, 1526, 1359, 747; HRMS (ES): calcd for $C_{23}H_{21}BrN_2O_2$ $[M]^+$: 436.0786; found: 436.0774.

Tricycle ***8e***. From 46 mg (0.14 mmol) of allene **5e**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **8e** (26 mg, 58%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.52 (d, 1H, J = 7.9 Hz), 7.31 (d, 1H, J = 8.2 Hz), 7.24 (td, 1H, J = 7.6, 1.1 Hz), 7.20 (s, 1H), 7.10 (td, 1H, J = 7.4, 1.3 Hz), 6.92 (t, 1H, J = 5.5 Hz), 6.03 (m, 1H), 5.17 (dt, 1H, J = 10.1, 1.3 Hz), 5.08 (dt, 1H, J = 17.1, 1.4 Hz), 4.71 (dd, 1H, J = 11.1, 3.4 Hz), 4.20 (m, 1H), 4.06 (dd, 1H, J = 11.1, 1.4 Hz), 3.81 (s, 3H), 3.23 (m, 2H), 1.88 (m, 1H), 0.99 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 162.9, 148.3, 137.7, 137.5, 130.7, 126.9, 122.7, 119.6, 118.5, 116.8, 116.6, 109.4, 100.6, 72.8, 47.0, 43.1, 29.5, 28.6, 20.2 (2C); IR ($CHCl_3$, cm^{-1}): ν 3398 (NH), 2930, 1685, 1524, 1369; HRMS (ES): calcd for $C_{20}H_{24}N_2O_2$ $[M]^+$: 324.1838; found: 324.1843.

Tricycle ***8f***. From 30 mg (0.09 mmol) of allene **5f**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound **8f** (29 mg, 98%) as a colorless solid; mp 181–182 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 8.57 (s, 1H), 7.63 (d, 2H, J = 7.6 Hz), 7.48 (d, 1H, J = 7.9 Hz), 7.28 (m, 4H), 7.21 (s, 1H), 7.07 (m, 2H), 6.02 (m, 1H), 5.15 (dt, 1H, J = 10.0, 1.4 Hz), 5.04 (dt, 1H, J = 17.0, 1.4 Hz), 4.76 (dd, 1H, J = 11.1, 3.3 Hz), 4.19 (m, 1H), 4.07 (dd, 1H, J = 11.1, 1.5 Hz), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 160.6, 147.8, 137.7, 137.6, 130.6, 129.0 (2C), 126.9, 124.4, 123.1, 119.8 (2C), 119.7, 118.7, 117.3, 117.0, 109.5, 101.7, 73.0, 55.4, 43.1, 29.6; IR ($CHCl_3$, cm^{-1}): ν 3397, 2930, 1684, 1523, 1353, 754, 701; HRMS (ES): calcd for $C_{22}H_{20}N_2O_2$ $[M]^+$: 344.1525; found: 344.1518.

General Procedure for the Gold-Catalyzed Hydroarylation of *β*-Lactam-Tethered Allenyl Indoles 6. Preparation of Tetrahydroazeto-azocino[3,4-*b*]indol-2-ones 9 and Hexahydroazeto-azepino[3,4-*b*]indol-2-ones 10. The appropriate allene **6** (1.0 mmol) was added to a stirred solution of [AuClIPr] (0.05 mmol) and $AgSbF_6$ (0.05 mmol) in 1,2-dichloroethane (13.0 mL) under argon. The resulting mixture was stirred at 90 °C under microwave irradiation until disappearance of the starting material (TLC). After filtration through a pad of Celite, the mixture was extracted with ethyl acetate (3 × 5 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure tetracyclic compounds **9** and **10**.

Tetracycle ***9a***. From 58 mg (0.21 mmol) of allene **6a**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **9a** (34 mg, 59%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.60 (d, 1H, J = 7.8 Hz), 7.28 (d, 1H, J = 7.3 Hz), 7.22 (td, 1H, J = 8.1, 1.2 Hz), 7.13 (td, 1H, J = 7.3, 1.4 Hz), 6.08 (m, 1H), 5.34 (m, 1H), 5.07 (d, 1H, J = 4.2 Hz), 4.92 (d, 1H, J = 4.4 Hz), 4.77 (d, 1H, J = 18.5 Hz), 3.98 (dd, 1H, J = 14.7, 7.4 Hz), 3.70 (s, 3H), 3.61 (d, 1H, J = 18.5 Hz), 3.35 (m, 1H), 3.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 167.4, 136.9, 131.6, 129.5, 127.1, 123.1, 121.8, 119.3, 115.3, 115.3, 108.8, 87.8, 58.3 (2C), 42.6, 29.9, 20.6; IR ($CHCl_3$, cm^{-1}): ν 2935, 1750, 1132, 929; HRMS (ES): calcd for $C_{17}H_{18}N_2O_2$ $[M]^+$: 282.1368; found: 282.1372.

Tetracycle ***9b***. From 85 mg (0.27 mmol) of allene **6b**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **9b** (59 mg, 70%) as a colorless solid; mp 158–159 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.54 (dd, 1H, J = 1.7, 0.7 Hz), 7.16 (d, 1H, J = 0.6 Hz), 7.15 (d, 1H, J = 1.7 Hz), 6.03 (m, 1H), 5.35 (m, 1H), 5.04 (d, 1H, J = 4.5 Hz), 4.91 (d, 1H, J = 4.4 Hz), 4.76 (d, 1H, J = 18.4 Hz), 3.95 (dd, 1H, J = 14.8, 7.2 Hz), 3.67 (s, 3H), 3.61 (d, 1H, J = 18.3 Hz), 3.34 (s, 3H), 3.23 (dd, 1H, J = 14.8, 9.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 167.2, 135.2, 131.3, 131.1, 128.0, 125.1, 123.3, 122.0, 117.5, 114.9, 109.8, 85.7, 58.4, 58.1, 42.6, 30.1, 20.6; IR ($CHCl_3$, cm^{-1}): ν 2939, 1753, 1138, 933; HRMS (ES): calcd for $C_{17}H_{17}ClN_2O_2$ $[M]^+$: 316.0979; found: 316.0990.

Tetracycle ***9c***. From 49 mg (0.16 mmol) of allene **6c**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **9c** (26 mg, 53%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.16 (d, 1H, J = 8.9 Hz), 7.02 (d, 1H, J = 2.3 Hz), 6.87 (dd, 1H, J = 8.8, 2.4 Hz), 6.09 (m, 1H), 5.34 (m, 1H), 5.05 (br s, 1H), 4.91 (br s, 1H), 4.75 (d, 1H, J = 18.5 Hz), 3.95 (dd, 1H, J = 14.9, 7.3 Hz), 3.88 (s, 3H), 3.67 (s, 3H), 3.61 (m, 1H), 3.32 (s, 3H), 3.27 (dd, 1H, J = 14.7, 9.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 167.4, 154.1, 132.2, 131.4, 130.0, 127.2, 123.2, 114.8, 112.1, 109.6, 99.8, 85.7, 58.4 (2C), 56.0), 42.6, 30.1, 20.7; IR ($CHCl_3$, cm^{-1}): ν 2939, 1752, 1127, 945; HRMS (ES): calcd for $C_{18}H_{20}N_2O_3$ $[M]^+$: 312.1474; found: 312.1481.

Tetracycle ***10a***. From 35 mg (0.12 mmol) of allene **6d**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **10a** (12 mg, 35%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.48 (d, 1H, J = 7.9 Hz), 7.29 (m, 1H), 7.22 (td, 1H, J = 8.2, 1.2 Hz), 7.11 (td, 1H, J = 7.3, 1.1 Hz), 6.09 (m, 1H), 5.17 (dt, 1H, J = 10.1, 2.7 Hz), 5.15 (m, 1H), 5.05 (dt, 1H, J = 17.0, 1.6 Hz), 4.96 (dd, 1H, J = 4.5, 1.6 Hz), 4.15 (m, 1H), 4.06 (m, 1H), 3.67 (s, 3H), 3.38 (s, 3H), 3.28 (m, 1H), 2.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 166.4, 159.7, 138.4, 131.9, 127.3, 121.7, 119.2, 118.0, 116.8, 115.3, 115.5, 108.8, 85.9, 57.9, 56.1, 37.9, 36.9, 30.5, 29.7; IR ($CHCl_3$, cm^{-1}): ν 2940, 1748, 1129, 930; HRMS (ES): calcd for $C_{18}H_{20}N_2O_2$ $[M]^+$: 296.1525; found: 296.1531.

Tetracycle ***10b***. From 39 mg (0.12 mmol) of allene **6e**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **10b** (13 mg, 33%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.42 (dd, 1H, J = 1.8, 0.6 Hz), 7.18 (d, 1H, J = 0.6 Hz), 7.17 (d, 1H, J = 1.9 Hz), 6.06 (m, 1H), 5.18 (dt, 1H, J = 10.1, 1.6 Hz), 5.12 (d, 1H, J = 4.5 Hz), 5.03 (dt, 1H, J = 17.0, 1.6 Hz), 4.94 (dd, 1H, J = 4.5, 1.6 Hz), 4.10 (m, 1H), 3.97 (m, 1H), 3.64 (s, 3H), 3.39 (s, 3H), 3.25 (m, 1H), 2.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 166.3, 138.1, 135.4, 133.4, 128.3, 125.1, 121.9, 117.6, 117.1, 115.2, 109.8, 85.9, 58.0, 56.0, 37.9, 36.9, 31.7, 30.7; IR ($CHCl_3$, cm^{-1}): ν 2947, 1751, 1133, 928; HRMS (ES): calcd for $C_{18}H_{19}ClN_2O_2$ $[M]^+$: 330.1135; found: 330.1135.

Tetracycle ***10c***. From 102 mg (0.31 mmol) of allene **6f**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **10c** (37 mg, 36%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.19 (d, 1H, J = 8.6 Hz), 6.90 (m, 1H), 6.88 (dd, 1H, J = 8.6, 2.5 Hz), 6.08 (m, 1H), 5.17 (dt, 1H, J = 10.1, 1.5 Hz), 5.12 (d, 1H, J = 4.4 Hz), 5.06 (dt, 1H, J = 17.0, 1.7 Hz), 4.95 (dd, 1H, J = 4.5, 1.5 Hz), 4.12 (m, 1H), 3.99 (m, 1H), 3.85 (s, 3H), 3.63 (s, 3H), 3.36 (s, 3H), 3.27 (m, 1H), 2.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 166.4, 154.1, 138.3, 132.5, 132.4, 127.6, 116.8 117.1, 114.9, 111.7, 109.5, 100.2, 85.9, 57.8, 56.1, 56.0, 37.9, 37.0, 31.8, 30.7; IR ($CHCl_3$, cm^{-1}): ν 2947, 1751, 1139, 926; HRMS (ES): calcd for $C_{19}H_{22}N_2O_3$ $[M]^+$: 326.1630; found: 326.1632.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of the ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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Stereoselective synthesis of strained cage compounds *via* gold-catalyzed allene functionalization†

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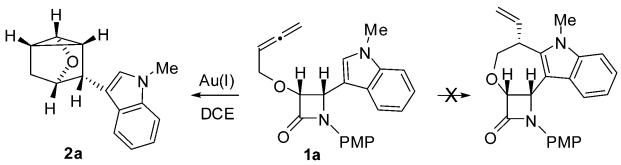
The diastereoselective synthesis of strained adducts that show cage-like structures has been accomplished directly from allenyl-β-lactams through gold catalysis.

The last decade has witnessed dramatic growth in the number of reactions catalyzed by gold complexes.[1] On the other hand, allenes[2] and β-lactams[3] have independently shown interesting reactivities and selectivities. In particular, gold-based complexes are suitable catalysts for the formation of polycyclic azetidinone.[4] Herein, we present a novel and unanticipated reactivity in gold catalysis starting from 3-allenyl 4-aryl(alkenyl) β-lactams.

Allenyl-β-lactam **1a** was initially chosen to study the possibility of an allene–aryl coupling. The allene functionality of starting substrate **1a** efficiently reacted under gold catalysed conditions, but unexpectedly the 2-azetidinone ring also disappeared in the final product **2a**, which reveals a highly complex cage structure (Table 1). The reaction efficiency varied considerably depending on the ligand, counter-anion, and temperature. $AuCl_3$, AuCl, and [(PPh_3)AuOTf] all failed to catalyse this reaction (Table 1, entries 1–3). Our catalyst screening led to the identification of [AuClIPr]/$AgSbF_6$ as the most suitable promoter. Among all the solvents examined, 1,2-dichloroethane (DCE) proved to be the best choice. The gold-catalysed reaction was sluggish at room temperature and after three days provided the product in a low yield (19%) (Table 1, entry 4). To our delight, the combined use of [IPrAuCl] (5 mol%) and $AgSbF_6$ (5 mol%) in refluxing DCE after 30 min resulted in an increased 75% yield for adduct **2a** (Table 1, entry 5). Applying microwave irradiation at 90 °C returned the best result, affording strained cage compound **2a** in 83% yield in just 10 min (Table 1, entry 6). The reaction of allene **1a** using Gagosz' catalyst [$(Ph_3P)AuNTf_2$] did not lead to complete consumption of starting **1a**, providing adduct **2a** in low yield (Table 1, entry 7). The yield could not be improved by using [IPrAuNTf$_2$] or [IPrAuOTf], or [IPrAuCl]/$AgBF_4$ as the catalyst (Table 1, entries 8–10).

Table 1 Catalyst screening for the gold-catalysed unpredictable reaction of 3-allenyl 4-[(indol-3-yl)] 2-azetidinone **1a** to afford cage adduct **2a**. PMP = 4-$MeOC_6H_4$



Entry	Catalyst	*T* (°C)	Time (h)	Yield[a] (%)
1	$AuCl_3$	20	24	—
2	AuCl	20	24	—
3	[(PPh_3)AuCl]/AgOTf	20	24	—
4	[AuClIPr][b]/$AgSbF_6$	20	72	**2a** (19)
5	[AuClIPr]/$AgSbF_6$	84	0.5	**2a** (75)
6	[AuClIPr]/$AgSbF_6$	90	0.16	**2a** (83)[c]
7	[$(Ph_3P)AuNTf_2$]	84	1.5	**2a** (12)
8	[AuClIPr]/$AgNTf_2$	84	0.5	**2a** (29)
9	[AuClIPr]/AgOTf	84	0.5	—
10	[AuClIPr]/$AgBF_4$	84	0.5	**2a** (67)

[a] Yields of pure, isolated products with correct analytical and spectral data. [b] IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [c] Reaction runs under microwave irradiation.

No advantage is gained from changing the 4-methoxyphenyl (PMP) substituent at N1 to a phenyl moiety, because the phenyl analogue was a poor participant.[5] Having the optimized conditions, we then studied the scope of the protocol by examining substitution on the indole moiety of the allenyl 4-indolyl β-lactams **1**. Introduction of substituents onto the aryl ring of **1** did not influence the efficiency of the reaction. For example, substrates **1b** and **1c** lead directly to the corresponding adducts

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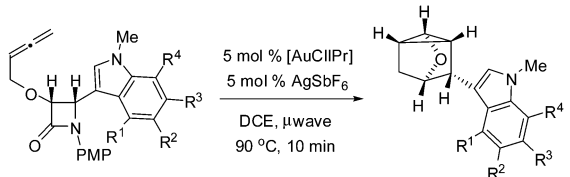
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data of new compounds, and copies of NMR spectra. CCDC 960487. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6cc03779h



1a R^1 = H, R^2 = H, R^3 = H, R^4 = H — **2a** (83%)
1b R^1 = H, R^2 = Br, R^3 = H, R^4 = H — **2b** (64%)
1c R^1 = NO_2, R^2 = H, R^3 = H, R^4 = H — **2c** (85%)
1d R^1 = H, R^2 = MeO, R^3 = H, R^4 = H — **2d** (74%)
1e R^1 = H, R^2 = H, R^3 = H, R^4 = Me — **2e** (57%)
1f R^1 = H, R^2 = H, R^3 = iPr, R^4 = H — **2f** (60%)

Scheme 1 Synthesis of strained cage compounds **2a–f**.

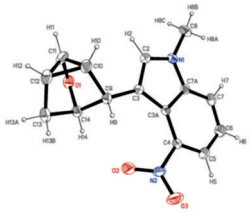
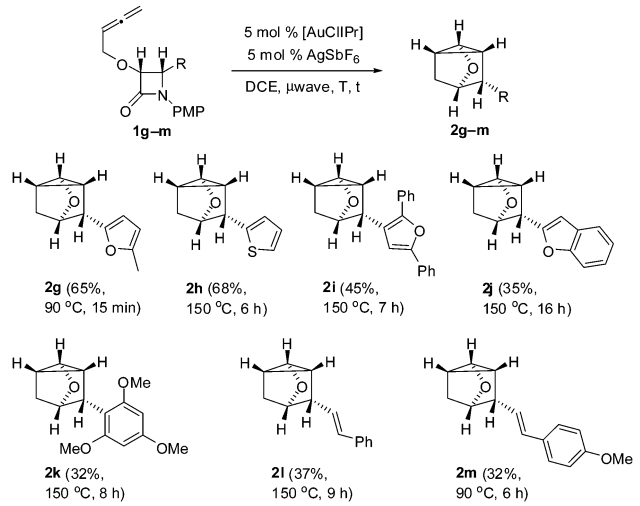


Fig. 1 ORTEP drawing of 5-indolyl-3-oxatricyclo[2.2.1.$0^{2,6}$]heptane **2c**.

2b and **2c** in good yields after exposure to 5 mol% of [AuClIPr]/$AgSbF_6$ (Scheme 1). It was found that introduction of electron-donating groups at the 5-, 6-, and 7-positions of the indole ring was fully tolerated (Scheme 1; **2d–f**). The single crystal XRD structure of nitro derivative **2c** unambiguously confirmed its strained oxa-cage nature (Fig. 1).[6,7] Notably, five new contiguous stereogenic centers have been created in a totally diastereoselective fashion in just a single operation.

The construction of compounds bearing novel structures in a predictable and selective way is a major challenge in modern chemistry. In particular, the molecular architecture of strained cage compounds **2** is appealing.[7] To this end, we set out to investigate the scope of this reaction by variation of the C4-substituent at the β-lactam ring. The electronic nature of the aromatic rings of precursors **1** did have a strong influence on the above reaction. For example, 3-allenyl 4-aryl β-lactams **1** possessing electron-withdrawing substituents, such as 4-nitrophenyl, or π-deficient heterocycles, such as pyridine, failed. We observed that a variety of hetaryl, aryl, and alkenyl moieties were well tolerated, because treatment of allenes **1g–m** with [AuClIPr]/$AgSbF_6$ in 1,2-dichloroethane under microwave irradiation gave the rearrangement reaction. The gold salt specifically promoted the generation of the desired cage adducts **2g–m** (Scheme 2). Complete conversion was observed by TLC and ^{1}H NMR analysis of the crude reaction mixtures of allenes **1**, and no side-products from competitive reactions were detected. Unfortunately, some decomposition was observed on sensitive cage adducts **2** during purification by flash chromatography, which may be responsible for the moderate isolated yields.

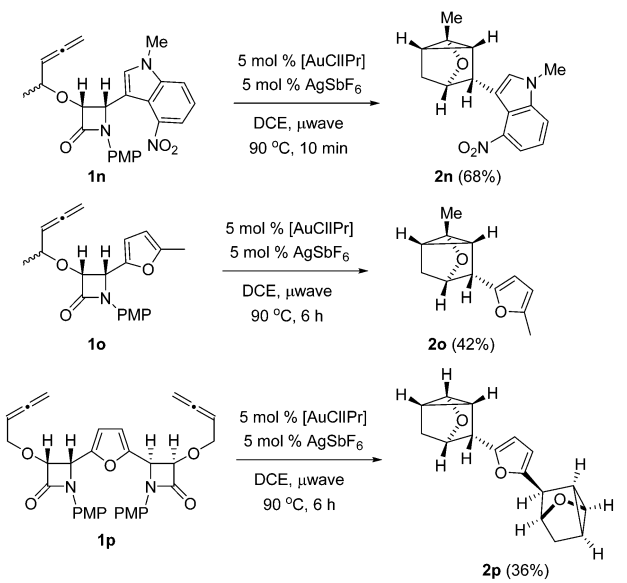
Branched allenes **1n** and **1o** were also well tolerated (Scheme 3). The methyl-substituted allene **1n** was converted into the constrained cage product **2n** in good yield while the reaction of its related derivative **1o** gave the corresponding adduct **2o** in



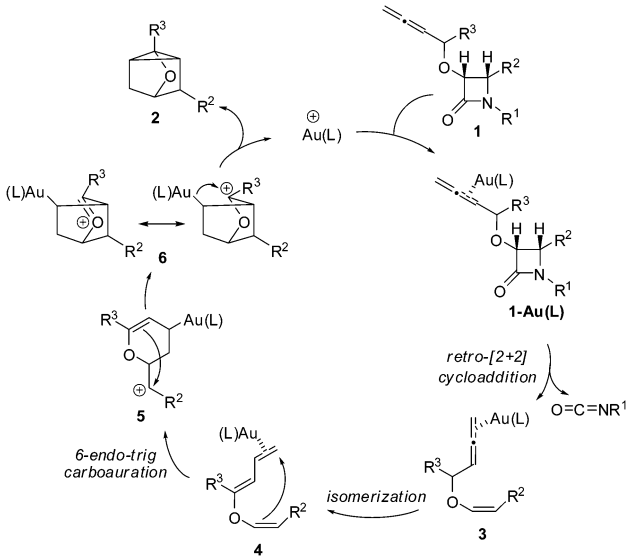
Scheme 2 Synthesis of strained cage compounds **2g–m**.

moderate yield. It is worthy of note that, despite that precursors **1n** and **1o** were mixtures of epimers that were not separated, both epimers at the methyl-substituted carbon converged in the formation of cage products **2n** and **2o**, which were formed as single isomers. The aim of the use of substrates **1n** and **1o** was double, namely, to allow for branched allenes to participate in the rearrangement as well as to obviate the need for the preparation of a stereoselective precursor. Our conditions were also effective for the two-fold reaction of bis(allenyl-β-lactam) **1p** (Scheme 3). This substrate provided in a totally selective fashion the desired bis(cage) adduct **2p** in moderate yield through a double reaction sequence.

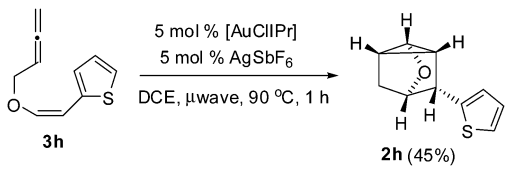
A possible pathway for the gold-catalysed generation of cage compounds **2** is outlined in Scheme 4. Initially, the formation of a **1**-Au(L) complex through coordination of the gold salt to the



Scheme 3 Synthesis of methyl-substituted cage adducts **2n**,**o** and bis(cage) adduct **2p**.



Scheme 4 Mechanistic explanation for the Au(I)-catalyzed synthesis of cage compounds **2** from allenyl-β-lactams **1**.



Scheme 5 Preparation of strained cage compound **2h** through tris-(cyclization) of (vinyloxy)buta-1,2-diene **3h** under gold catalysis.

internal allene double bond may be involved. Initially, (vinyloxy)-buta-1,2-dienes **3** could be formed through a retro-[2+2] alkene–isocyanate cycloaddition.[8] Next, allene-diene isomerization could lead to gold-complexed conjugated dienes **4**.[9,10] This path must be driven by relief of the strain associated with the four-membered ring upon forming highly conjugated polyene intermediates, enol ethers **4**. Species **4** undergo an intramolecular chemo- and regioselective carbocyclization reaction to produce (3,4-dihydro-2*H*-pyran-4-yl)gold carbenium species **5**. Activation of the exocyclic methylene position by a delocalized benzylic-like carbocation can induce selectively a new carbocyclization to bicyclic cations **6**. Species **6** are stabilized by the electron pair of the α heteroatom, which would facilitate the intramolecular nucleophilic addition of the gold-bonded carbon to the ion moiety. The result of this carbocyclization is the formation of cage compounds **2** with concurrent regeneration of the gold catalyst (Scheme 4).

According to the above mechanism, cage compounds **2** could be obtained from (vinyloxy)buta-1,3-dienes **4** or from (vinyloxy)buta-1,2-dienes **3** (*via* isomerisation to dienyl-vinyl ethers **4** and further cyclization). To gain insight into the mechanism, a proposed intermediate, the previously unknown polyene (vinyloxy)buta-1,2-diene **3h**, was synthesized (see the ESI† for details) and subjected to the standard conditions, resulting in the formation of cage adduct **2h** in a yield of 45% (Scheme 5). This fact clearly confirmed the crucial use of stable and readily prepared allenyl-β-lactams as masked dienyl-vinyl ethers in gold catalysis.[11]

Density functional theory (DFT) calculations[12] were carried out to gain more insight into the gold(I)-catalysed transformation

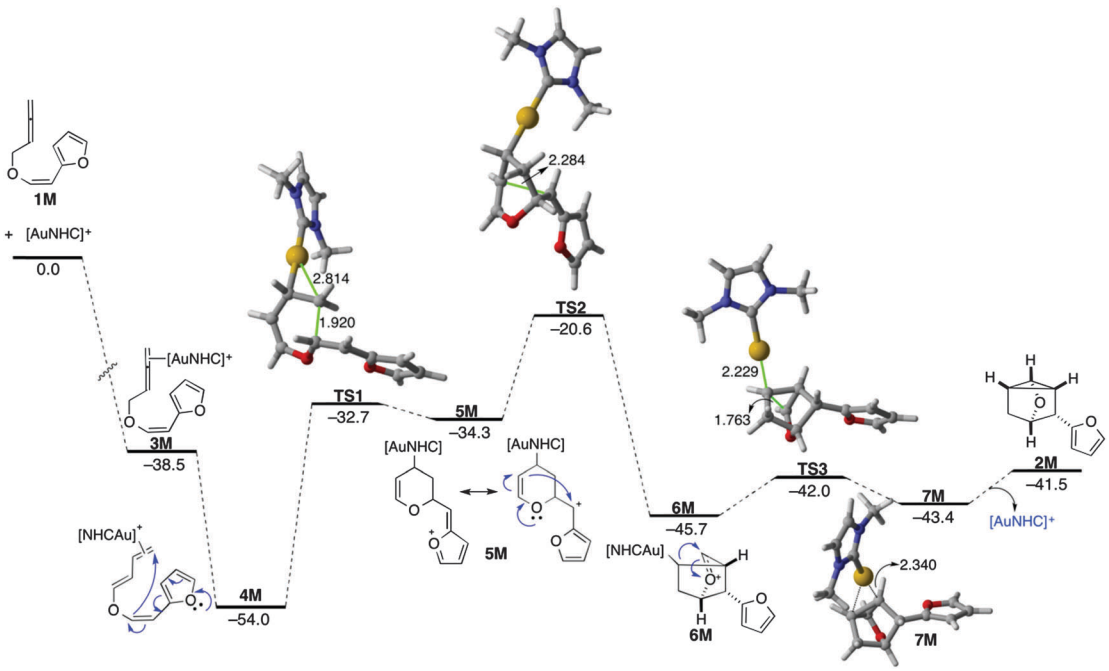


Fig. 2 Computed profile for the gold(I)-catalysed transformation of allenyl derivative **3M** into cage-compound **2M**. Bond lengths and relative free energies (ΔG_{298}, computed at 298 K) are given in angstroms and kcal mol^{-1}, respectively. NHC = 1,3-bis(methyl)-1,3-dihydro-2*H*-imidazol-2-ylidene. All data have been computed at the PCM(dichloroethane)-B3LYP-D3/def2-TZVP//PCM(dichloroethane)-B3LYP-D3/def2-SVP level.

of buta-1,2-dienes **3** into the cage compounds **2**. To this end, we explored the corresponding reaction profile involving the furyl-substituted buta-1,2-diene **1M** and the model [1,3-bis(methyl)-1,3-dihydro-2*H*-imidazol-2-ylidene]-Au^+ catalyst leading to the cage compound **2M** (Fig. 2).

The process begins with the highly exergonic coordination of the allenyl moiety of **1M** to the gold(I) catalyst to form the π-complex **3M** (ΔG_R = −38.5 kcal mol^{-1}). From the data in Fig. 2, it can be seen that this species readily isomerizes into the thermodynamically more stable 1,3-diene derivative **4M** (ΔG_R = −15.5 kcal mol^{-1}) in a transformation which is very likely mediated by the catalyst counteranion according to previously reported gold-catalysed allenyl-diene isomerizations.[9,10] Intermediate **4M** experiences then a carbocyclization reaction leading to the carbocationic intermediate **5M** through transition state **TS1** ($\Delta G^{\neq}$ = 21.3 kcal mol^{-1}). This saddle point is associated with the formation of a new C–C bond and occurs in a regioselective manner from the nucleophilic attack of the carbon atom at the β-position of the furyl moiety to the distal CH_2 fragment of the diene. This finding provides further support to the experimental observation that only electron-rich aryl groups, which greatly increase the nucleophilicity of this β-carbon atom, are able to participate in the transformation. Carbenium intermediate **5M** evolves into oxacarbenium derivative **6M** *via* **TS2** ($\Delta G^{\neq}$ = 13.7 kcal mol^{-1}) in a highly exergonic reaction (ΔG_R = −25.1 kcal mol^{-1}). The saddle point **TS2** is associated with the formation of the second C–C bond as a result of the intramolecular nucleophilic addition of the carbon atom at the β-position of the oxygen atom (*i.e.* enol ether) to the benzylic-like carbocationic centre of **5M**. A new intramolecular carbocyclization reaction derived from the easy ($\Delta G^{\neq}$ = 3.7 kcal mol^{-1}) nucleophilic attack from the carbon atom directly attached to the metal fragment to the carbon atom of the oxacarbenium moiety of **6M** *via* **TS3** finishes the process. This reaction step results in the formation of the cage-compound **7M** where the gold(I)-catalyst is only weakly bonded to the cyclopropyl moiety. Final release of the catalyst would produce the observed tricyclic compound **2M**, regenerating the catalyst. Therefore, our DFT calculations suggest that the transformation of allenyl-derivatives **3**, readily formed from the fragmentation of the corresponding β-lactams **1**, into the observed cage-compounds **2** involves an initial isomerization reaction to the thermodynamically more stable 1,3-butadiene coordinated Au(I)-complexes followed by three consecutive intramolecular carbocyclization reactions.

In conclusion, the diastereoselective synthesis of strained adducts which show cage-like structures has been accomplished directly from allenyl-β-lactams through gold catalysis. Both experimental results and DFT calculations support the involvement of (vinyloxy)buta-1,2-diene intermediates readily formed upon fragmentation of the β-lactam ring.

Support for this work by the MINECO and FEDER (Projects CTQ2012-33664-C02-01, CTQ2012-33664-C02-02, CTQ2013-44303-P, CTQ2014-51912-REDC, CTQ2015-65060-C2-1-P, and CTQ2015-65060-C2-2-P) is gratefully acknowledged. S. C. thanks MEC for a predoctoral contract. We thank Dr M. R. Torres for X-ray analysis.

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9 For studies of the gold-catalyzed allene-diene isomerization, see: (*a*) J.-M. Chen, C.-J. Chang, Y.-J. Ke and R.-S. Liu, *J. Org. Chem.*, 2014, **79**, 4306; (*b*) A. Basak, K. Chakrabarty, A. Ghosh and G. K. Das, *J. Org. Chem.*, 2013, **78**, 9715.
10 For the gold-catalyzed isomerization of alkynes to 1,3-dienes with the intermediacy of allenes, see: Z. Wang, Y. Wang and L. Zhang, *J. Am. Chem. Soc.*, 2014, **136**, 8887.
11 Highly stable β-lactam precursors **1** are readily prepared in good overall yields beginning from the appropriate imine by Staudinger reaction with acetoxyacetyl chloride in the presence of Et_3N, followed by sequential transesterification, treatment with propargyl bromide, and final Crabbé reaction. (Vinyloxy)buta-1,2-dienes **3** are relatively unstable precursors. Besides, their preparation required nine steps from propargyl alcohol, while just a four-step sequence is needed for the preparation of β-lactam allenes **1**. In addition, the aryl moiety in β-lactam precursors **1** came from aldehydes while for the introduction of the arene functionality into enol ethers **3** a less available boronic acid is required. The atom-efficiency for the gold-catalyzed reaction is higher starting from alkenes **3**. However, taking into account that for the preparation of (vinyloxy)buta-1,2-dienes **3** the incorporation and further cleavage of a TIPS group, a TfO moiety, and a boronic acid $B(OH)_2$ are required, the atom economy of the overall process is favourable for the use of β-lactam allenes.
12 All the calculations reported herein were performed at the PCM(dichloroethane)-B3LYP-D3/def2-TZVP//PCM(dichloroethane)-B3LYP-D3/def2-SVP level. See Computational Details in the ESI†.

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Acid-Catalyzed Synthesis of α,β-Disubstituted Conjugated Enones by a Meyer–Schuster-Type Rearrangement in Allenols

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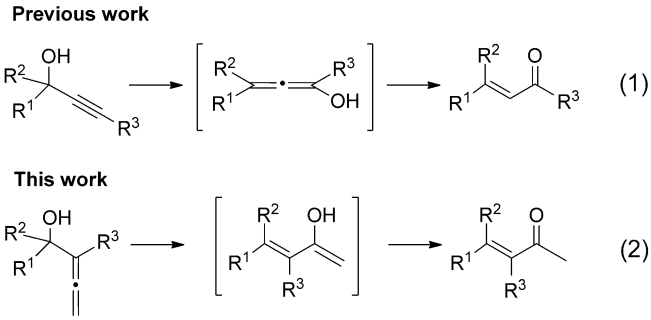
Abstract: A novel, direct and simple methodology to gain access to α,β-disubstituted conjugated enones from α-allenols in a sustainable metal catalysis context, considering the inexpensiveness and environmentally friendliness of iron(III) species and protons, has been developed.

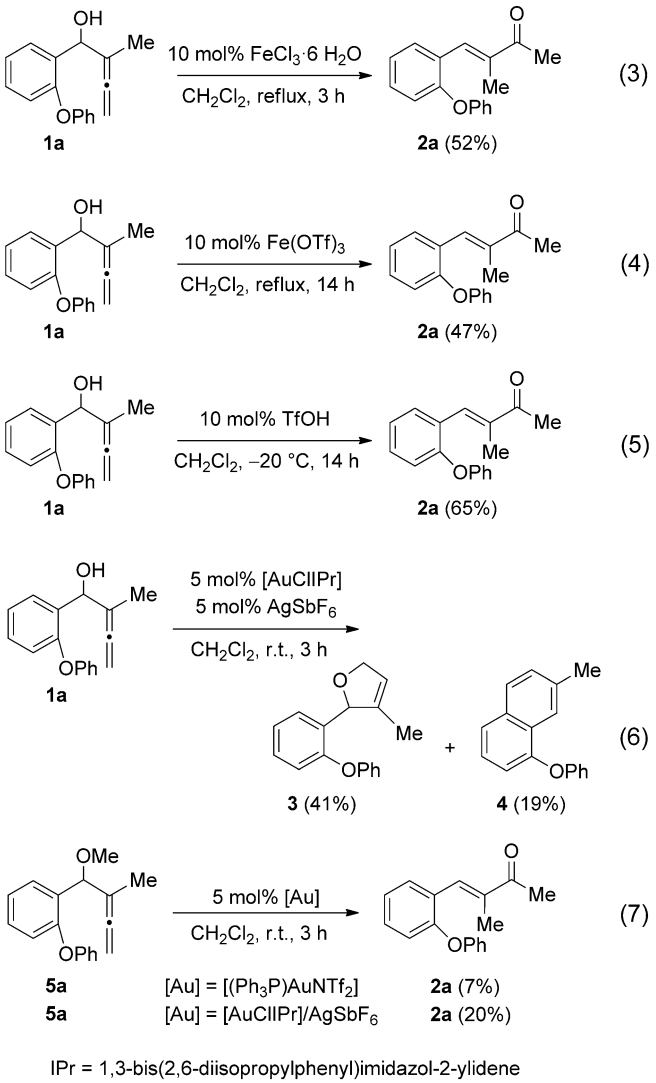
Keywords: alcohols; allenes; Brønsted acids; homogeneous catalysis; Lewis acids



Scheme 1. Alkynol *versus* allenol isomerization.

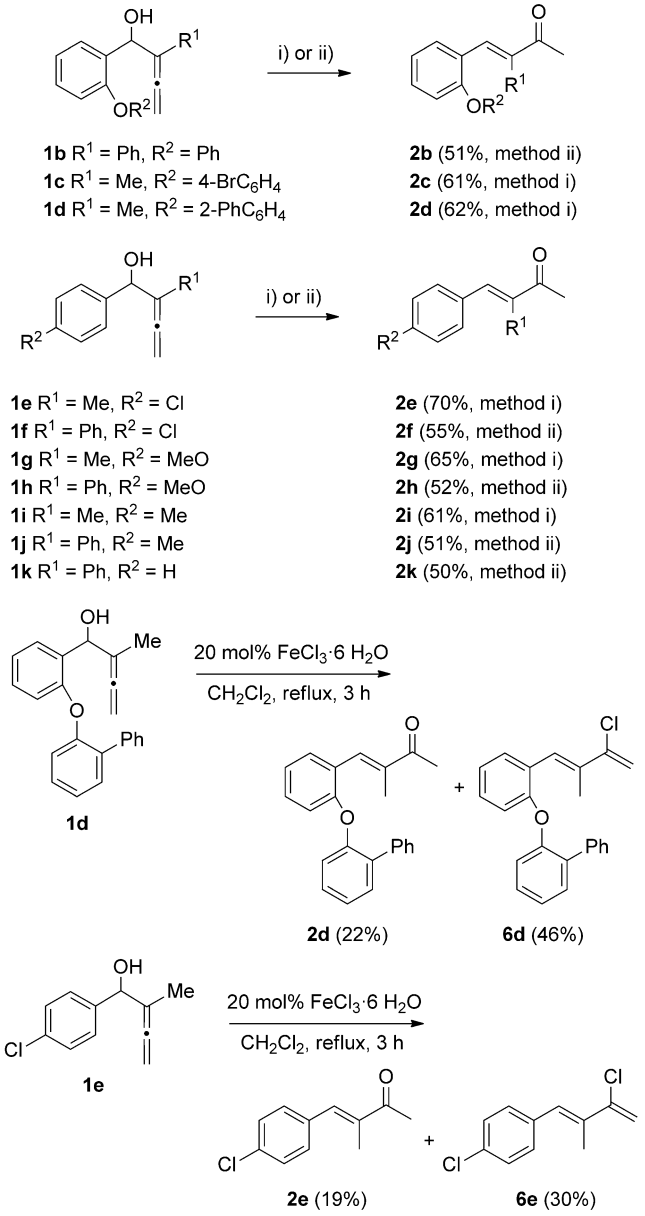
The use of α,β-unsaturated ketones as starting materials to prepare a variety of compounds, as well as the presence of this structural unit in a large number of biologically active natural products have led to increased recent interest in methods for preparing such compounds.[1] Classical methods such as aldol condensation and olefination strategies present serious drawbacks. Thus, harsh conditions and modest yields are usually encountered in the aldol condensation, while the generation of noxius waste by-products coupled with low atom economy are disadvantages of Wittig-type reactions. Besides, these traditional protocols usually require strong basic conditions, which may be incompatible with selectivity control as well as sensitive functional groups. An alternative method for the synthesis of α,β-unsaturated ketones is the Meyer–Schuster rearrangement [Scheme 1, Eq. (1)], which starts from propargylic alcohols and consists in a formal 1,3-hydroxy shift followed by tautomerization.[2] In this regard, the rearrangement of allenic alcohols may be a possible solution to produce α,β-unsaturated ketones with high reaction efficiency; although this achievement has not yet been fully accomplished.[3] Besides, the allenol rearrangement could provide competitive advantages, because in contrast with the alkynol rearrangement, the allenic version could afford internally substituted conjugated enones. On the other hand, iron-catalyzed processes have attracted recent attention because iron is one of the most inexpensive and environmentally benign metals on earth.[4] Following up on our combined interest in the area of allenes and metals,[5] and considering the economic attractiveness and the environmentally friendliness of iron species, we chose to study the iron-catalyzed reaction of α-allenols as a sustainable metal-catalyzed route to access α,β-disubstituted conjugated enones [Scheme 1, Eq. (2)].

Starting allenols **1** were readily prepared in good overall yield from the appropriate carbaldehyde through a regioselective indium-mediated Barbier-type carbonyl-allenylation reaction in aqueous media using our methodology.[6] Initially, we were attempting the iron-catalyzed cycloisomerization reaction of allenol **1a**. Unexpectedly, the alkenone **2a** was obtained using either iron(III) chloride hexahydrate or iron(III) triflate. Considering the abundance and non-

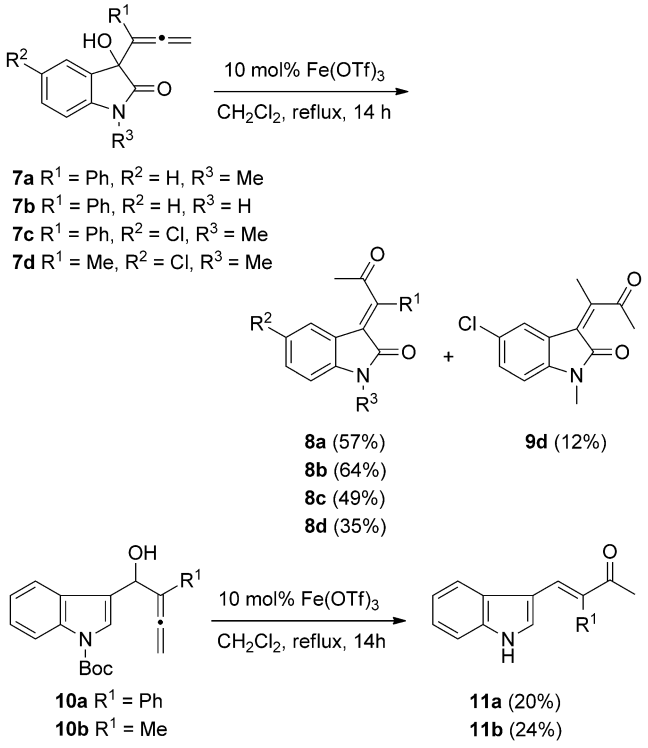


Scheme 2. Divergent metal-catalyzed rearrangement of allenol derivatives **1a** and **5a**.

toxicity of iron(III) species, we became interested in developing an allenol-based Meyer–Schuster rearrangement methodology for the preparation of functionalized α,β-unsaturated ketones. The reaction was next optimized by screening solvent and temperature. A 52% yield of α,β-unsaturated ketone **2a** was obtained through the use of $FeCl_3{\cdot}6H_2O$ (10 mol%) and dichloromethane as the solvent at 40 °C [Scheme 2, Eq. (3)]. A similar result was encountered through the use of catalytic amounts of $Fe(OTf)_3$ [Scheme 2, Eq. (4)]. This reaction could also be catalyzed by $Bi(OTf)_3$ and $In(OTf)_3$, but with diminished effectiveness. Different Lewis acid catalysts such as $InCl_3$, $ZnCl_2$, and AgOTf were found to be completely ineffective in carrying out any reorganization of the allenol. A Brønsted acid such as the super acid TfOH was shown to efficiently transform **1a** into **2a** at low temperature [Scheme 2, Eq. (5)]. To check whether gold complexes are good catalysts for this rearrangement, a reaction of allenol **1a** in the presence of $[(Ph_3P)AuNTf_2]$ was also carried out.[7] The reaction does take a different course, with a separable mixture of oxycyclization and carbocyclization adducts **3** and **4** being obtained [Scheme 2, Eq. (6)].[8] It was interesting at this point to test the reactivity of a protected allenol moiety under gold-catalyzed conditions. When the hydroxy functionality in **1a** was protected in the form of a methyl ether as in **5a**, the gold-catalyzed Meyer–Schuster type rearrangement occurred,[9] but in low yield [Scheme 2, Eq. (7)].



Scheme 3. Acid-catalyzed rearrangement of allenols **1**. *Reagents and conditions:* i) 10 mol% TfOH, CH_2Cl_2, –20 °C, 14 h; ii) 10 mol% $Fe(OTf)_3$, CH_2Cl_2, reflux, 14 h.

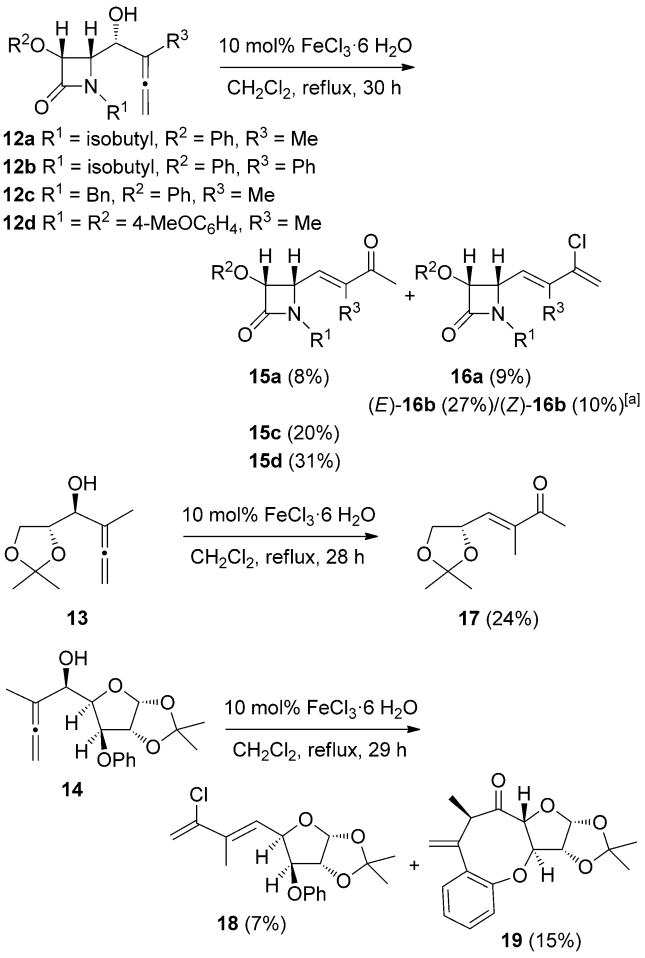


Scheme 4. $Fe(OTf)_3$-catalyzed rearrangement of indole-linked allenols **7** and **10**.

With the optimized conditions in hand, we then examined the generality of this acid-catalyzed rearrangement protocol in α-allenols **1**. When allenols **1c–1e**, **1g**, and **1i** were tested as precursors using triflic acid catalysis, they furnished the corresponding reorganization products **2c–2e**, **2g**, and **2i** (Scheme 3). Complete conversion was observed for phenyl-substituted allenes **1b**, **1f**, **1h**, **1j**, and **1k** but complicated reaction mixtures were obtained. Competing reactions lead to the exclusion of the above allenols as efficient substrates for the TfOH-promoted reaction. Fortunately, $Fe(OTf)_3$ did afford the corresponding α,β-unsaturated ketones **2b**, **2f**, **2h**, **2j**, and **2k** in fair yields (Scheme 3). The reactions were selective and only Meyer–Schuster adducts were formed, with no trace of isomeric oxycyclization products. Electron-withdrawing and electron-donating substituents on the aryl ring were tolerated with only little influence on the reactivity (Scheme 3). Chlorodienes **6** were often obtained as important components during the $FeCl_3{\cdot}6H_2O$-catalyzed reaction of α-allenols **1** (Scheme 3).

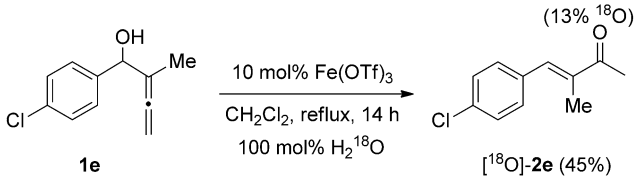
3-Methyleneindolin-2-ones are not only recognized as versatile intermediates in organic synthesis,[10] but also exhibit interesting biological activities.[11] Consequently, the iron-catalyzed stereoselective synthesis of 3-alkenyloxindole **8a** from 2-indolinone-tethered allenol **7a** under similar conditions is noteworthy (Scheme 4). Allenic *NH*-indolinone **7b** smoothly provided the 3-alkenyloxindole rearranged adduct **8b** as sole product (Scheme 4), it was thus apparent that substitution at the nitrogen atom of the heterocycle should have little effect upon the reactivity of the allenol moiety. Allenic 5-chloroindolinone **7c** smoothly provided the rearranged adduct **8c** in reasonable yield (Scheme 4). The major product for the methyl-substituted allenol **7d** was assigned to be the *E* form, α,β-unsaturated ketone **8d**, the unexpected *Z* isomer **9d** being the minor component (Scheme 4).[12] The iron-catalyzed rearrangement reaction of (indol-3-yl)-α-allenols **10a** and **10b** afforded *N*-Boc deprotected α,β-unsaturated ketones **11a** and **11b** in modest yields (Scheme 4).[13]

Unfortunately, enantiopure allenols **12–14** derived from aliphatic aldehydes were not as rewarding as their aromatic counterparts. Neither $Fe(OTf)_3$ nor TfOH reacted well, because decomposition adducts were detected. Interestingly, the use of $FeCl_3{\cdot}6H_2O$ afforded identifiable products. However, this variation led to less efficiency in terms of chemical yields of the ketone derivatives **15** and **17** (Scheme 5). Chloro-

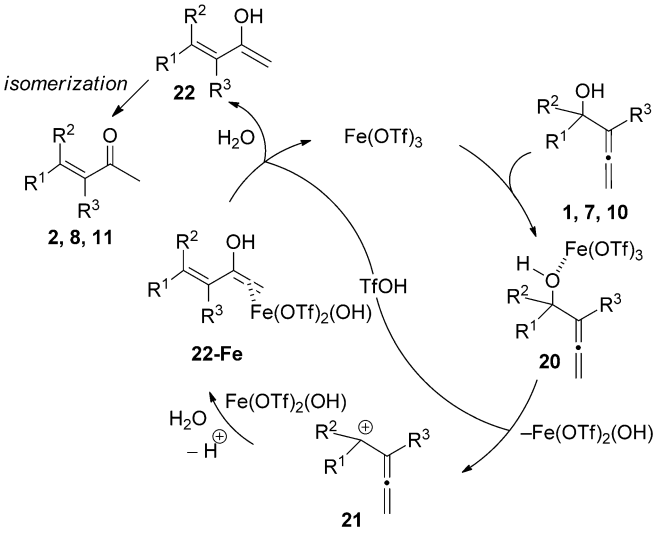


[a] The reaction was carried out using 20 mol% $FeCl_3$.

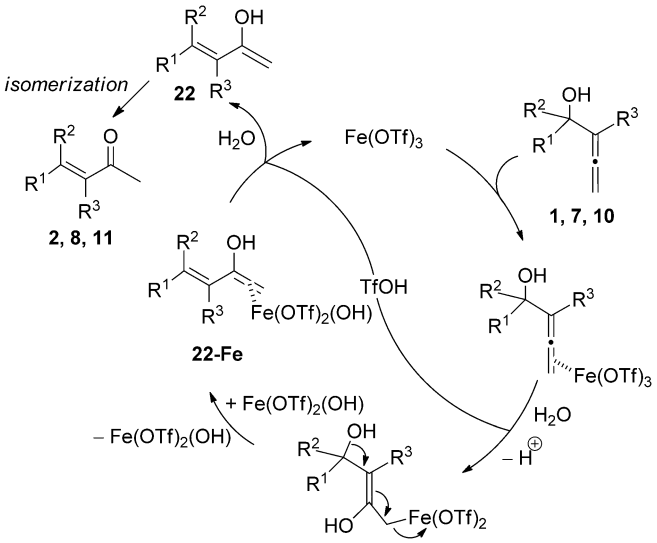
Scheme 5. $FeCl_3$-catalyzed rearrangement of allenols **12–14**.



Scheme 6. Labelling experiment.



Scheme 7. Mechanistic explanation for the iron-catalyzed rearrangement of allenols through elimination–addition.



Scheme 8. Mechanistic explanation for the iron-catalyzed rearrangement of allenols through addition–elimination.

dienes **16a**, **16b**, and **18** were obtained in appreciable amounts. Surprisingly, tricycle **19** was obtained as major component from allene sugar derivative **14** (Scheme 5). Importantly, no erosion of the stereochemical integrity was observed in enantiopure products **15**–**19**.

In order to interpret the rearrangement reaction outcome in a more useful manner, an ^{18}O-labelling experiment was planned. ^{18}O-incorporation was monitored as an indicator of a mechanistic scenario that involves an indirect intermolecular 1,3-shift of the OH group. Mass spectrometric analysis of the product of reaction of allenol **1e** under $Fe(OTf)_3$ catalysis in presence of 100 mol% $H_2{}^{18}O$ showed that the α,β-unsaturated ketone **2e** was partially ^{18}O-labelled (Scheme 6), revealing that the carbonylic oxygen atom may arise from external H_2O.

The high stereoselectivity of the rearrangement which occurs by (*E*)-alkene formation, is independent of the stereochemistry of the starting α-allenol (racemic or enantiopure). This fact and the labelling experiment may indicate a stepwise path with the participation of carbocationic species. A possible reaction pathway leading to α,β-unsaturated ketones from α-allenols was proposed as shown in Scheme 7. $Fe(OTf)_3$ acts as a Lewis acid interacting with the alcohol group in the allenol moiety. Initial σ-coordination of the metal to the hydroxy group of allenols **1**, **7**, and **10**, leads to complexes **20**. Separation of the alcohol group by $Fe(OTf)_3$ generates allenic cation **21**, which would facilitate the nucleophilic addition of water to the carbenium ion, thus leading to a metallated intermediate **22-Fe**. Next, demetallation yields neutral dienol species **22** and regenerates the iron catalyst. Finally, isomerization could generate α,β-unsaturated ketones **2**, **8**, and **11** (Scheme 7). However, taking all the experiments into account, an alternative addition–elimination mechanism scenario as sketched in Scheme 8 cannot be completely ruled out.

In conclusion, a novel, direct and simple methodology to gain access to α,β-disubstituted conjugated enones from α-allenols in a sustainable metal catalysis context, considering the inexpensiveness and environmentally friendliness of iron(III) species and protons, has been developed.

Experimental Section

General Methods

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300 or Bruker AMX-500. NMR spectra were recorded in $CDCl_3$ solutions unless otherwise stated. Chemical shifts are given in ppm relative to TMS (^1H, 0.0 ppm), or $CDCl_3$ (^{13}C, 77.0 ppm). Coupling constants *J* are expressed in Hertz (multiplicity: s = singulet, d = doublet, dd = double doublet, t = triplet, dt = double triplet, q = quadruplet, quint = quintuplet, sext = sextuplet, sept = septuplet, m = multiplet). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electrospray mode (ES) unless otherwise

stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. Specific rotations $[\alpha]_D$ are given in 10^{-1} deg $cm^2 g^{-1}$ at 20 °C, and the concentration (c) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

Typical Procedure for the TfOH-Catalyzed Rearrangement Reaction of α-Allenols 1

To a cooled solution of the appropriate allenol **1** (1.0 mmol) in dichloromethane (10 mL) at −20 °C, TfOH (0.10 mmol) was added. The reaction mixture was stirred at −20 °C until the starting material disappeared as indicated by TLC. Water (1 mL) was added, and the mixture was allowed to warm to room temperature before being partitioned between dichloromethane and water. The organic extract was concentrated under vacuum, and purified by flash column chromatography eluting with ethyl acetate/hexanes mixtures. Spectroscopic and analytical data for pure forms of compounds **2** are given below.[14]

α,β-Unsaturated ketone 2a: From 134 mg (0.53 mmol) of α-allenol **1a**, chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound **2a** as a colorless oil; yield: 88 mg (65%); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.66 (s, 1H, =CH), 7.45 (dd, 1H, J = 7.7, 1.3 Hz, Ar), 7.34 (t, 2H, J = 7.6 Hz, Ar), 7.31 (td, 1H, J = 7.4, 1.6 Hz, Ar), 7.18 (t, 1H, J = 7.9 Hz, Ar), 7.11 (t, 1H, J = 7.4 Hz, Ar), 6.97 (m, 3H, Ar), 2.36 (s, 3H, COMe), 2.01 (t, 3H, J = 1.2 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 202.2 (CO), 157.2, 155.0, 138.6, 134.9 (=CH), 130.6 (Ar, CH), 130.0 (Ar, CH), 129.8 (Ar, 2CH), 127.7, 123.3 (Ar, CH), 123.3 (Ar, CH), 119.1 (Ar, CH), 118.1 (Ar, 2CH), 25.7 (Me), 12.3 (Me); IR ($CHCl_3$): ν = 3066, 1668 (CO), 1484, 1238, 753 cm^{-1}; HR-MS (ES): m/z = 252.1142, calcd. for $C_{17}H_{16}O_2$ $[M]^+$: 252.1150.

α,β-Unsaturated ketone 2c: From 108 mg (0.33 mmol) of α-allenol **1c**, chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **2c** as a colorless oil; yield: 67 mg (61%); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.60 (s, 1H, =CH), 7.44 (m, 1H, Ar), 7.43 (d, 2H, J = 9.0 Hz, Ar), 7.34 (td, 1H, J = 7.7, 1.7 Hz, Ar), 7.20 (td, 1H, J = 7.9, 1.0 Hz, Ar), 6.96 (dd, 1H, J = 8.1, 1.1 Hz, Ar), 6.84 (d, 2H, J = 9.0 Hz, Ar), 2.37 (s, 3H, COMe), 1.99 (t, 3H, J = 1.4 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 198.6 (CO), 159.1, 157.8, 138.9, 134.4 (=CH), 132.8 (Ar, 2CH), 130.8 (Ar, CH), 130.2 (Ar, CH), 128.7, 123.9 (Ar, CH), 119.8 (Ar, 2CH), 119.2 (Ar, CH), 116.4, 25.8 (Me), 13.0 (Me); IR ($CHCl_3$): ν = 3066, 1667 (CO), 1477, 1234, 756 cm^{-1}; HR-MS (ES): m/z = 330.0245, calcd. for $C_{17}H_{15}BrO_2$ $[M]^+$: 330.0255.

α,β-Unsaturated ketone 2d: From 238 mg (0.73 mmol) of allenol **1d**, chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **2d** as a colorless oil; yield: 147 mg (62%); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.60 (s, 1H, =CH), 7.49 (m, 3H, Ar), 7.32 (m, 4H, Ar), 7.24 (t, 3H, J = 7.6 Hz, Ar), 7.07 (t, 1H, J = 7.5 Hz, Ar), 6.90 (dd, 1H, J = 8.0, 1.2 Hz, Ar), 6.85 (d, 1H, J = 7.3 Hz, Ar), 2.36 (s, 3H, COMe), 1.94 (d, 3H, J = 1.3 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 200.4 (CO), 155.4, 153.4, 153.2, 137.6, 136.8, 135.2 (Ar, CH), 133.4, 131.4 (Ar, CH), 130.4 (Ar, CH), 129.8 (Ar, CH), 129.1 (Ar, 2CH), 128.7 (Ar, CH), 128.0 (Ar, 2CH), 127.3 (Ar, CH), 124.3 (Ar, CH), 122.5 (Ar, CH), 119.7 (Ar, CH), 117,3 (=CH), 25.7 (Me), 12.9 (Me); IR ($CHCl_3$): ν = 3061, 1666 (CO), 1476, 1223, 745, 695 cm^{-1}; HR-MS (ES): m/z = 328.1473, calcd. for $C_{23}H_{20}O_2$ $[M]^+$: 328.1463.

α,β-Unsaturated ketone 2e: From 340 mg (1.75 mmol) of allenol **1e**, chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave compound **2e** as a colorless oil; yield: 239 mg (70%); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.38 (d, 1H, J = 0.9 Hz), 7.32 (d, 2H, J = 8.9 Hz), 7.28 (d, 2H, J = 8.8 Hz), 2.39 (s, 3H), 1.96 (d, 3H, J = 1.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 200.0, 138.1, 134.4, 130.9 (2C), 129.5, 128.8 (2C), 128.7, 25.9, 13.0; IR ($CHCl_3$): ν = 3070, 1668 (CO), 751, 696 cm^{-1}; HR-MS (ES): m/z = 194.0497, calcd. for $C_{11}H_{11}ClO$ $[M]^+$: 194.0498.

α,β-Unsaturated ketone 2g: From 40 mg (0.21 mmol) of α-allenol **1g**, chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent gave compound **2g** as a colorless oil; yield: 26 mg (65%); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.40 (s, 1H), 7.34 (d, 2H, J = 8.8 Hz), 6.88 (d, 2H, J = 8.9 Hz), 3.78 (s, 3H), 2.38 (s, 3H), 2.00 (d, 3H, J = 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 200.3, 139.6, 135.9, 131.6 (2C), 129.8, 128.5, 113.9 (2C), 55.4, 28.5, 12.9; IR ($CHCl_3$): ν = 3069, 1670 (CO), 1481, 1236, 751, 696 cm^{-1}; HR-MS (ES): m/z = 190.0998, calcd. for $C_{12}H_{14}O_2$ $[M]^+$: 190.0994.

α,β-Unsaturated ketone 2i: From 100 mg (0.57 mmol) of α-allenol **1i**, chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **2i** as a colorless oil; yield: 61 mg (61%); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.42 (s, 1H), 7.27 (d, 2H, J = 8.0 Hz), 7.15 (d, 2H, J = 8.0 Hz), 2.38 (s, 3H), 2.32 (s, 3H), 1.99 (d, 3H, J = 1.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 200.0, 140.3, 139.1, 137.2, 133.2, 130.2 (2C), 129.6 (2C), 26.3, 22.0, 13.4; IR ($CHCl_3$): ν = 3074, 1672 (CO), 1482, 1233, 752, 697 cm^{-1}; HR-MS (ES): m/z = 174.1047, calcd. for $C_{12}H_{14}O$ $[M]^+$: 174.1045.

Typical Procedure for the $Fe(OTf)_3$-Catalyzed Rearrangement Reaction of α-Allenols 1, 7, and 10

To a solution of the appropriate allenol **1** (1.0 mmol) in dichloromethane (10 mL), $Fe(OTf)_3$ (0.10 mmol) was added. The reaction mixture was stirred at reflux temperature until the starting material disappeared as indicated by TLC. After filtration through a pad of Celite, the mixture was concentrated under vacuum, and purified by flash column chromatography eluting with ethyl acetate/hexanes mixtures. Spectroscopic and analytical data for pure forms of compounds **2**, **8**, **9**, and **11** are given below.

α,β-Unsaturated ketone 2b: From 68 mg (0.22 mmol) of α-allenol **1b**, chromatography of the residue using hexanes/ethyl acetate (7:1) as eluent gave compound **2b** as a colorless oil; yield: 36 mg (51%); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.94 (s, 1H, =CH), 7.37 (m, 6H, Ar), 7.15 (m, 3H, Ar), 7.01 (d, 2H, J = 8.6 Hz, Ar), 6.87 (d, 1H, J = 8.1 Hz, Ar), 6.76 (d, J = 4.1 Hz, Ar), 2.33 (s, 3H, COMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 199.4 (CO), 157.4, 156.1, 156.0, 142.0, 133.6 (=CH), 130.9 (Ar, CH), 130.3 (Ar, CH), 129.9 (Ar, 2CH), 129.8 (Ar, 2CH), 128.7 (Ar, 2CH), 127.8 (Ar, CH), 126.6, 123.4 (Ar, CH), 123.0 (Ar, CH), 118.9 (Ar, CH), 118.6 (Ar, 2CH), 27.4(Me); IR ($CHCl_3$): ν = 3061, 1675

(CO), 1482, 1233, 752, 695 cm^{-1}; HR-MS (ES): m/z = 314.1306, calcd. for $C_{22}H_{18}O_2$ $[M]^+$: 314.1307.

α,β-Unsaturated ketone 2f: From 200 mg (0.78 mmol) of α-allenol **1f**, chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave compound **2f** as a colorless oil; yield: 110 mg (55%); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.59 (s, 1H, =CH), 7.42 (m, 3H, Ar), 7.16 (m, 2H, Ar), 7.14 (d, 2H, J = 8.6 Hz, Ar), 6.96 (d, 2H, J = 8.5 Hz, Ar), 2.30 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 199.1 (CO), 141.3, 137.2 (=CH), 136.6, 135.1, 133.1, 132.0 (Ar, 2CH), 129.4 (Ar, 2CH), 129.2 (Ar, 2CH), 128.5 (Ar, 2CH), 128.1 (Ar, CH), 28.0 (Me); IR ($CHCl_3$): ν = 2930, 1662 (CO), 1457, 1090, 810 cm^{-1}; HR-MS (ES): m/z = 256.0659, calcd. for $C_{16}H_{13}OCl$ $[M]^+$: 256.0655.

α,β-Unsaturated ketone 2h: From 95 mg (0.38 mmol) of allenol **1h**, chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound **2h** as a colorless oil; yield: 49 mg (52%); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.55 (s, 1H), 7.34 (m, 3H), 7.11 (dd, 2H, J = 8.0, 1.9 Hz), 6.90 (d, 2H, J = 8.9 Hz), 6.61 (d, 2H, J = 8.9 Hz), 3.68 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 199.2, 160.5, 138.8, 138.7, 137.5, 132.7 (2C), 129.6 (2C), 129.2 (2C), 128.5, 127.2, 113.8 (2C), 55.2, 27.9; IR ($CHCl_3$): ν = 3075, 1670 (CO), 1471, 1225, 742, 692 cm^{-1}; HR-MS (ES): m/z = 252.1157, calcd. for $C_{17}H_{16}O_2$ $[M]^+$: 252.1150.

α,β-Unsaturated ketone 2j: From 220 mg (0.93 mmol) of α-allenol **1j**, chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **2j** as a colorless oil; yield. 112 mg (51%); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.64 (s, 1H, =CH), 7.40 (m, 3H, Ar), 7.19 (dd, 2H, J = 7.8, 2.0 Hz, Ar), 6.99 (d, 2H, J = 8.3 Hz, Ar), 6.93 (d, 2H, J = 8.3 Hz, Ar), 2.32 (s, 3H, Me), 2.28 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 199.3 (CO), 140.0, 139.6, 139.0 (=CH), 137.2, 131.7, 130.9 (Ar, 2CH), 129.5 (Ar, 2CH), 129.0 (Ar, 4CH), 127.8 (Ar, CH), 27.9 (Me), 21.3 (Me); IR ($CHCl_3$): ν = 2900, 1653 (CO), 1434, 815 cm^{-1}; HR-MS (ES): m/z = 236.1199, calcd. for $C_{17}H_{16}O$ $[M]^+$: 236.1201.

α,β-Unsaturated ketone 2k: From 161 mg (0.72 mmol) of α-allenol **1k**, chromatography of the residue using hexanes/ethyl acetate (30:1) as eluent gave compound **2k** as a colorless oil; yield: 80 mg (50%); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.66 (s, 1H, =CH), 7.42 (m, 3H, Ar), 7.18 (m, 5H, Ar), 7.05 (d, 2H, J = 7.7 Hz, Ar), 2.33 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 199.3 (CO), 140.9, 138.8 (=CH), 136.9, 134.6, 130.8 (Ar, 2CH), 129.5 (Ar, 2CH), 129.2 (Ar, CH), 129.0 (Ar, 2CH), 128.2 (Ar, 2CH), 127.9 (Ar, CH), 27.9 (Me); IR ($CHCl_3$): ν = 2915, 1660 (CO), 1426, 1024 cm^{-1}; HR-MS (ES): m/z = 222.1041, calcd. for $C_{16}H_{14}O$ $[M]^+$: 222.1045.

α,β-Unsaturated ketone 8a: From 140 mg (0.50 mmol) of α-allenol **7a**, chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **8a** as a colorless oil; yield: 79 mg (57%); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.43 (m, 5H), 7.16 (m, 1H), 6.72 (d, 1H, J = 7.7 Hz), 6.68 (m, 2H), 3.17 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 204.4, 167.1, 151.8, 145.0, 133.4, 130.5, 130.2, 129.7 (2C), 128.7, 128.3 (2C), 123.6, 122.4, 121.1, 108.7, 29.5, 26.4; IR ($CHCl_3$): ν = 2932, 1705 (CO), 1610 (CO), 1482, 754, 696 cm^{-1}; HR-MS (ES): m/z = 277.1093, calcd. for $C_{18}H_{15}NO_2$ $[M]^+$: 277.1103.

α,β-Unsaturated ketone 8b: From 60 mg (0.23 mmol) of α-allenol **7b**, chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound **8b** as a colorless oil; yield: 38 mg (62%); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.44 (m, 5H), 7.10 (m, 1H), 6.75 (d, 1H, J = 7.7 Hz), 6.66 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.7, 150.4, 147.9, 141.7, 132.9, 131.1, 130.2, 129.9, 129.4 (2C), 127.8 (2C), 123.7, 122.0, 121.5, 109.9, 29.0; IR ($CHCl_3$): ν = 2936, 1706 (CO), 1606 (CO), 1482, 755, 695 cm^{-1}; HR-MS (ES): m/z = 263.0956, calcd. for $C_{17}H_{13}NO_2$ $[M]^+$: 263.0946.

α,β-Unsaturated ketone 8c: From 125 mg (0.38 mmol) of allenol **7c**, chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave compound **8c** as a colorless oil; yield: 63 mg (49%); ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.50 (m, 4H, Ar), 7.20 (m, 2H, Ar), 6.73 (d, 1H, J = 8.3 Hz, Ar), 6.70 (d, 1H, J = 2.1 Hz, Ar), 3.24 (s, 3H, NMe), 2.48 (s, 3H, COMe); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 203.4 (CO), 166.4 (CO), 153.0, 143.0, 132.4, 130.3 (Ar, CH), 129.7 (Ar, CH), 129.5 (Ar, 2CH), 128.3 (Ar, CH), 127.7 (Ar, 2CH), 127.4, 123.3 (Ar, CH), 123.0, 122.0, 109.1 (Ar, CH), 28.9 (Me), 26.1 (NMe); IR ($CHCl_3$): ν = 2924, 1707 (CO), 1608 (CO), 1485, 755, 698 cm^{-1}; HR-MS (ES): m/z = 311.0724, calcd. for $C_{18}H_{14}ClNO_2$ $[M]^+$: 311.0713.

α,β-Unsaturated ketones 8d and 9d: From 111 mg (0.45 mmol) of α-allenol **7d**, chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave the less polar compound **8d** (yield: 32 mg, 35%) and the more polar compound **9d** '(yield: 11 mg, 12%). *α,β-Unsaturated ketone* **8d:** Colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.26 (dd, 1H, J = 8.3, 1.9 Hz, Ar), 7.14 (d, 1H, J = 2.0 Hz, Ar), 6.74 (d, 1H, J = 8.3 Hz, Ar), 3.23 (s, 3H, NMe), 2.62 (s, 3H, Me), 2.50 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 205.2 (CO), 167.3 (CO), 151.6, 141.1, 129.2 (Ar, CH), 127.6, 122.6 (Ar, CH), 121.5, 120.8, 108.9 (Ar, CH), 28.4 (NMe), 25.9 (Me), 15.7 (Me); IR ($CHCl_3$): ν = 2925, 1715 (CO), 1604 (CO), 1475, 756 cm^{-1}; HR-MS (ES): m/z = 249.0567, calcd. for $C_{13}H_{12}ClNO_2$ $[M]^+$: 249.0557. *α,β-Unsaturated ketone* **9d:** Colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.50 (d, 1H, J = 2.0 Hz, Ar), 7.30 (dd, 1H, J = 8.3, 1.9 Hz, Ar), 6.77 (d, 1H, J = 8.3 Hz, Ar), 3.20 (s, 3H, NMe), 2.49 (s, 3H, Me), 2.36 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 206.3 (CO), 170.3 (CO), 165.9, 142.7, 129.1 (Ar, CH), 127.6, 123.9 (Ar, CH), 123.0, 109.1 (Ar, CH), 28.6 (NMe), 25.9 (Me), 17.4 (Me); IR ($CHCl_3$): ν = 2920, 1706 (CO), 1600 (CO), 1461, 736 cm^{-1}; HR-MS (ES): m/z = 249.0564, calcd. for $C_{13}H_{12}ClNO_2$ $[M]^+$: 249.0557.

α,β-Unsaturated Ketone 11a: From 94 mg (0.26 mmol) of α-allenol **10a**, chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent gave compound **11a** as a colorless oil; yield: 18 mg (20%); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.30 (s, 1H, NH), 8.12 (m, 2H, Ar), 7.97 (s, 1H, Ar), 7.72 (m, 3H, Ar), 7.49 (m, 3H, Ar + =CH), 7.35 (m, 2H, Ar), 2.36 (s, 3H, COMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 172.8 (CO), 171.3, 129.5 (=CH), 129.1, 128.9 (Ar, 2CH), 128.7 (Ar, CH), 128.1 (Ar, CH), 127.4 (2C), 127.3 (Ar, CH), 125.1 (Ar, CH), 123.2 (Ar, CH), 118.4 (Ar, CH), 115.2 (Ar, CH), 110.7 (Ar, CH), 28.0 (Me); IR ($CHCl_3$): ν = 3370 (NH), 3057, 1734 (CO) 1457, 1152, 754 cm^{-1}; HR-MS (ES): m/z = 261.1166, calcd. for $C_{18}H_{15}NO$ $[M]^+$: 261.1154.

α,β-Unsaturated Ketone 11b: From 82 mg (0.27 mmol) of α-allenol **10b**, chromatography of the residue using hexanes/

ethyl acetate (6:1) as eluent gave compound **11b** as a colorless oil; yield: 19 mg (26%); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.64 (s, 1H, NH), 7.91 (s, 1H, =CH), 7.82 (d, 1H, J = 7.1 Hz, Ar), 7.59 (d, 1H, J = 2.8 Hz, Ar), 7.46 (d, 1H, J = 7.1 Hz, Ar), 7.29 (m, 2H, Ar), 2.55 (s, 3H, COMe); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 172.6 (CO), 135.4, 132.8, 131.1 (Ar, CH), 129.4, 126.1 (Ar, CH), 124.5, 123.3 (Ar, CH), 120.9 (Ar, CH), 118.5 (Ar, CH), 111.4 (Ar, CH), 25.5 (Me), 19.6 (Me); IR ($CHCl_3$): ν = 3314 (NH), 1708 (CO) 1460, 1245, 748 cm^{-1}; HR-MS (ES): m/z = 199.1005, calcd. for $C_{13}H_{13}NO$ $[M]^+$: 199.0997.

Typical Procedure for the Iron-Catalyzed Rearrangement Reaction of α-Allenols 1 and 12–14

To a solution of the appropriate allenol **1** or **12–14** (1.0 mmol) in dichloromethane (10 mL), $FeCl_3{\cdot}6H_2O$ (0.10 mmol or 0.20 mmol) was added. The reaction mixture was stirred at reflux temperature until the starting material disappeared as indicated by TLC. After filtration through a pad of Celite, the mixture was concentrated under vacuum, and purified by flash column chromatography eluting with ethyl acetate/hexanes mixtures. Spectroscopic and analytical data for pure forms of compounds **2**, **6**, and **15–19** are given below.

α,β-Unsaturated ketone 2d and chlorodiene 6d: From 238 mg (0.73 mmol) of allenol **1d**, chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave the less polar compound **6d** (yield: 114 mg, 46%) and the more polar compound **2d** (yield: 52 mg (22%). *Chlorodiene* **6d:** colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.48 (dd, 2H, J = 7.0, 1.5 Hz, Ar), 7.36 (td, 2H, J = 7.6, 1.6 Hz, Ar), 7.28 (t, 1H, J = 7.0 Hz, Ar), 7.15 (m, 3H, Ar), 7.02 (td, 1H, J = 7.8, 1.6 Hz, Ar), 6.88 (td, 1H, J = 7.6, 1.0 Hz, Ar), 6.81 (dd, 1H, J = 8.0, 1.2 Hz, Ar), 6.67 (dd, 1H, J = 8.2, 1.0 Hz, Ar), 6.34 (s, 1H, =CH), 5.08 (d, 1H, J = 1.1 Hz, =C*H*H), 4.91 (d, 1H, J = 1.1 Hz, =CH*H*), 1.92 (d, 3H, J = 1.4 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 154.9, 153.8, 139.8, 137.8, 136.2, 133.2, 131.2 (Ar, CH), 130.3 (Ar, CH), 129.7, 129.3 (Ar, 2CH), 128.6 (Ar, CH), 128.3 (Ar, CH), 128.1 (Ar, 2CH), 127.2 (Ar, CH), 124.7 (Ar, CH), 123.7 (Ar, CH), 122.7 (Ar, CH), 119.3 (Ar, CH), 117.7 (=CH), 115.3 (=CH_2), 23.3 (Me); IR ($CHCl_3$): ν = 3060, 1477, 1430, 1228, 744, 694 cm^{-1}; HR-MS (ES): m/z = 346.1138, calcd. for $C_{23}H_{19}ClO$ $[M]^+$: 346.1124.

α,β-Unsaturated ketone 2e and chlorodiene 6e: From 340 mg (1.75 mmol) of allenol **1e**, chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave the less polar compound **6e** (yield: 112 mg, 30%) and the more polar compound **2e** (yield: 65 mg, 19%). *Chlorodiene* **6e:** colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.22 (d, 2H, J = 8.6 Hz), 7.17 (d, 2H, J = 8.8 Hz), 6.21 (d, 1H, J = 1.2 Hz), 5.21 (d, 1H, J = 1.3 Hz), 5.05 (d, 1H, J = 1.3 Hz), 1.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 139.6, 136.3, 135.0, 132.8, 130.0 (2C), 128.3 (2C), 128.1, 115.5, 23.7; IR ($CHCl_3$): ν = 3060, 1478, 745, 692 cm^{-1}; HR-MS (ES): m/z = 212.0143, calcd for $C_{11}H_{10}Cl_2$ $[M]^+$: 212.0160.

α,β-Unsaturated ketone 15a and chlorodiene 16a: From 101 mg (0.33 mmol) of allenol **12a**, chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave the less polar compound **16a** (yield: 10 mg, 9%) and the more polar compound **15a** (yield: 8 mg 8%). *α,β-Unsaturated ketone* **15a:** colorless oil; $[\alpha]_D$: +32.0 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.27 (t, 2H, J = 7.3 Hz, Ar), 7.00 (t, 1H, J = 7.4 Hz, Ar), 6.92 (d, 2H, J = 7.9 Hz, Ar), 6.55 (dd, 1H, J = 9.4, 1.3 Hz, =CH), 5.45 (d, 1H, J = 4.4 Hz, H3), 4.79 (dd, 1H, J = 9.4, 4.4 Hz, H4), 3.23 (dd, 1H, J = 14.0, 7.7 Hz, NCH*H*), 2.88 (dd, 1H, J = 14.0, 6.7 Hz, NC*H*H), 2.23 (s, 3H, COMe), 1.86 (m, 1H, CH isobut), 1.85 (d, 3H, J = 1.3 Hz, Me), 0.98 (d, 3H, J = 7.4 Hz, Me), 0.95 (d, 3H, J = 6.8 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 198.5 (CO), 165.4 (CO), 156.5, 142.8, 134.6 (=CH), 130.7 (Ar, 2CH), 122.5 (Ar, CH) 115.2 (Ar, 2CH), 81.1 (CH), 56.8 (CH), 48.7 (NCH_2), 26.5 (CH isobut), 24.6 (Me), 19.3 (Me), 19.3 (Me); IR ($CHCl_3$): ν = 1757 (CO), 1673 (CO), 1232, 754 cm^{-1}; HR-MS (ES): m/z = 301.1682, calcd. for $C_{18}H_{23}NO_3$ $[M]^+$: 301.1678. *Chlorodiene* **16a:** colorless oil; $[\alpha]_D$: +7.8 (c 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.28 (t, 2H, J = 7.3 Hz, Ar), 7.01 (t, 1H, J = 7.3 Hz, Ar), 6.98 (dd, 2H, J = 8.8, 1.1 Hz, Ar), 5.47 (dd, 1H, J = 9.8, 1.5 Hz, =CH), 5.45 (d, 1H, J = 1.3 Hz, =C*H*H), 5.29 (d, 1H, J = 4.4 Hz, H3), 5.14 (d, 1H, J = 1.2 Hz, =CH*H*), 4.76 (dd, 1H, J = 9.9, 4.5 Hz, H4), 3.16 (dd, 1H, J = 14.0, 7.9 Hz, NCH*H*), 2.88 (dd, 1H, J = 14.0, 6.7 Hz, NC*H*H), 1.92 (d, 3H, J = 1.5 Hz, Me),.1.88 (m, 1H, CH isobut), 0.95 (d, 3H, J = 6.9 Hz, Me), 0.92 (d, 3H, J = 6.7 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.8 (CO), 157.3, 142.5, 138.1, 129.5 (Ar, 2CH), 123.8 (Ar, CH), 122.2 (=CH), 115.7 (Ar, 2CH), 115.3 (=CH_2), 81.7 (CH), 57.3 (CH), 48.2 (NCH_2), 27.5 (CH isobut), 22. 6 (Me), 20.3 (Me), 20.3 (Me); IR ($CHCl_3$): ν = 3342 (OH), 1758 (CO), 1236, 756 cm^{-1}; HR-MS (ES): m/z = 319.1324, calcd. for $C_{18}H_{22}ClNO_2$ $[M]^+$: 319.1339.

Chlorodiene (*E*)-16b and chlorodiene (*Z*)-16b: From 140 mg (0.38 mmol) of allenol **12b**, chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave the less polar compound (*E*)-**16b** (yield: 41 mg, 27%) and the more polar compound (*Z*)-**16b** (yield: 15 mg, 10%). *Enol* (*E*)-**16b:** colorless oil; $[\alpha]_D$: +23.3 (c 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.22 (m, 4H, Ar), 7.18 (m, 3H, Ar), 6.91 (d, 2H, J = 7.7 Hz, Ar), 6.90 (m, 1H, Ar), 5.96 (d, 1H, J = 10.1 Hz, =CH), 5.69 (d, 1H, J = 1.0 Hz, =C*H*H), 5.33 (d, 1H, J = 4.4 Hz, H-3), 5.29 (d, 1H, J = 1.2 Hz, =CH*H*), 4.85 (dd, 1H, J = 9.9, 4.4 Hz, H-4), 3.12 (dd, 1H, J = 13.9, 7.6 Hz, NCH*H*), 2.89 (dd, 1H, J = 13.9, 6.9 Hz, NC*H*H), 1.86 (sept, 1H, J = 6.7 Hz, CH isobut), 0.89 (d, 3H, J = 6.7 Hz, Me), 0.86 (d, 3H, J = 6.6 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.6 (CO), 157.1, 145.9, 136.6, 135.9, 129.5 (Ar, 2CH), 128.8 (Ar, CH), 128.6 (Ar, 2CH), 126.7 (Ar, 2CH), 124.5 (=CH), 122.3 (Ar, CH), 118.6 (=CH_2), 115.5 (Ar, 2CH), 81.8 (CH), 58.0 (CH), 48.6 (NCH_2), 27.6 (CH isobut), 20.3 (Me), 20.3 (Me); IR ($CHCl_3$): ν = 3405 (OH), 3061, 1761 (CO), 1235, 757, 694 cm^{-1}; HR-MS (ES): m/z = 381.1508, calcd. for $C_{23}H_{24}ClNO_2$ $[M]^+$: 381.1496. *Enol* (*Z*)-**16b:** colorless oil; $[\alpha]_D$: +15.4 (c 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.42 (m, 4H, Ar), 7.26 (m, 3H, Ar), 7.14 (d, 2H, J = 7.4 Hz, Ar), 7.00 (m, 1H, Ar), 6.30 (d, 1H, J = 2.8 Hz, =CH), 5.69 (d, 1H, J = 1.6 Hz, =C*H*H), 5.26 (d, 1H, J = 1.6 Hz, =CH*H*), 5.08 (d, 1H, J = 4.2 Hz, H-3), 4.78 (dd, 1H, J = 4.1, 2.8 Hz, H-4), 3.33 (dd, 1H, J = 13.9, 8.0 Hz, NCH*H*), 3.12 (dd, 1H, J = 14.0, 6.6 Hz, NC*H*H), 2.00 (m, 1H, CH isobut), 1.04 (d, 3H, J = 6.7 Hz, Me), 0.99 (d, 3H, J = 6.7 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.1 (CO), 156.2, 145.3, 137.1, 132.2, 130.7 (Ar, CH), 129.5 (Ar, CH), 128.8 (Ar, CH), 128.5 (Ar,

2 CH), 128.0 (Ar, CH), 127.4 (Ar, CH), 125.6 (Ar, 2 CH), 124.9 (=CH), 121.7 (Ar, CH), 120.4 (=CH_2), 88.1 (CH), 60.7 (CH), 48.6 (NCH_2), 27.4 (CH isobut), 20.5 (Me), 20.5 (Me); IR ($CHCl_3$): ν = 3396 (OH), 3062, 1758 (CO), 1231, 760, 699 cm^{-1}; HR-MS (ES): m/z = 381.1481, calcd. for $C_{23}H_{24}ClNO_2$ $[M]^+$: 381.1496.

α,β-Unsaturated ketone 15c: From 28 mg (0.08 mmol) of α-allenol **12c**, chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave compound **15c** as a colorless oil; yield: 5 mg (20%); $[\alpha]_D$ =: +25.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.30 (m, 6 H, Ar), 7.03 (m, 2 H, Ar), 6.90 (d, 2 H, *J* = 7.9 Hz, Ar), 6.34 (dd, 1 H, *J* = 9.5, 1.3 Hz, =CH), 5.41 (d, 1 H, *J* = 4.5 Hz, H3), 4.65 (dd, 1 H, *J* = 9.5, 4.5 Hz, H4), 4.57 (d, 1 H, *J* = 14.8 Hz, NC*H*H), 4.29 (d, 1 H, *J* = 14.9 Hz, NCH*H*), 2.06 (s, 3 H, COMe), 1.64 (d, 3 H, *J* = 1.3 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 198.9 (CO), 164.7 (CO), 156.9, 142.4, 134.8, 134.5 (=CH), 129.6 (Ar, 2 CH), 129.0 (Ar, 2 CH), 128.7 (Ar, 2 CH), 128.3 (Ar, CH), 122.5 (Ar, CH), 115.2 (Ar, 2 CH), 81.8 (CH), 55.9 (CH), 45.2 (NCH_2), 25.5 (Me), 11.4 (Me); IR ($CHCl_3$): ν = 3063, 1760 (CO), 1682 (CO), 1234, 754, 699 cm^{-1}; HR-MS (ES): m/z = 335.1526, calcd. for $C_{21}H_{21}NO_3$ $[M]^+$: 335.1521.

α,β-Unsaturated ketone 15d: From 12 mg (0.03 mmol) of α-allenol **12d**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **15d** as a colorless oil; yield: 4 mg (31%); $[\alpha]_D$: +18.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.31 (d, 2 H, *J* = 9.1 Hz, Ar), 6.92 (d, 2 H, *J* = 9.2 Hz, Ar), 6.89 (d, 2 H, *J* = 9.1 Hz, Ar), 6.82 (d, 2 H, *J* = 9.1 Hz, Ar), 6.65 (dd, 1 H, *J* = 9.2, 1,3 Hz, =CH), 5.47 (d, 1 H, *J* = 4.8 Hz, H3), 5.17 (dd, 1 H, *J* = 9.2, 4.8 Hz, H4), 3.81 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 2.26 (s, 3 H, Me), 1.97 (d, 3 H, *J* = 1.5 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 197.2 (CO), 161.9 (CO), 156.8, 155.1, 151.1, 142.7, 135.3 (=CH), 130.4, 118.3 (Ar, 2 CH), 116.5 (Ar, 2 CH), 114.7 (Ar, 2 CH), 114.6 (Ar, 2 CH), 82.0 (CH), 56.4 (CH), 55.6 (OMe), 55. 5. (OMe), 25.7 (Me), 11.9 (Me); IR ($CHCl_3$): ν = 2924, 1755 (CO), 1675 (CO), 1508, 1247, 628 cm^{-1}; HR-MS (ES): m/z = 381.1578, calcd for $C_{22}H_{23}NO_5$ $[M]^+$: 381.1576.

α,β-Unsaturated ketone 17: From 158 mg (0.86 mmol) of α-allenol **13**, chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave compound **17** as a colorless oil; yield: 38 mg (24%); $[\alpha]_D$: +13.0 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 6.56 (dd, 1 H, *J* = 7.4, 1,3 Hz, =CH), 4.94 (q, 1 H, *J* = 7.5 Hz, OCH), 4.21 (dd, 1 H, *J* = 8.2, 6.3 Hz, C*H*H), 3.64 (dd, 1 H, *J* = 8.0, 7.6 Hz, CH*H*), 2.35 (s, 3 H, COMe), 1.82 (d, 3 H, *J* = 1.3 Hz, Me), 1.49 (s, 3 H, Me), 1.43 (s, 3 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 199.4 (CO), 139.4 (=CH), 109.9 (2 C), 73.1 (OCH_2), 68.7 (OCH), 26.6 (Me), 25.7 (Me), 25.5 (Me), 11.8 (Me); IR ($CHCl_3$): ν = 2927, 1720 (CO), 1257, 1098 cm^{-1}; HR-MS (ES): m/z = 184.1104, calcd. for $C_{10}H_{16}O_3$ $[M]^+$: 184.1099.

Chlorodiene 18 and tricycle 19: From 133 mg (0.42 mmol) of allenol **14**, chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave the less polar compound **19** (yield: 20 mg, 15%) and the more polar compound **18** (yield: 11 mg, 7%). *Chlorodiene* **18:** colorless oil; $[\alpha]_D$: −17.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.31 (t, 2 H, *J* = 7.5 Hz, Ar), 7.00 (t, 1 H, *J* = 7.5 Hz, Ar), 6.96 (d, 2 H, *J* = 7.7 Hz, Ar), 6.41 (d, 1 H, *J* = 7.3 Hz, =CH), 6.03 (d, 1 H, *J* = 3.8 Hz, H1), 5.46 (d, 1 H, *J* = 1.5 Hz, =C*H*H), 5.41 (d, 1 H, *J* = 1.5 Hz, =CH*H*), 5.14 (dd, 1 H, *J* = 8.0, 3.1 Hz, H4), 4.71 (d, 1 H, *J* = 4.0 Hz, H2), 4.64 (d, 1 H, *J* = 3.2 Hz, H3), 1.98 (d, 3 H, *J* = 1.0 Hz, Me), 1.60 (s, 3 H, Me), 1.35 (s, 3 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 157.1, 141.4, 135.8, 129.7 (Ar, 2 CH), 124.8 (=CH), 121.7 (Ar, CH), 115.3 (Ar, 2 CH), 113.6 (=CH_2), 111.8, 104.8 (CH), 82.7 (CH), 81.5 (CH), 75.9 (CH), 26.8 (Me), 26.2 (Me), 15.0 (Me); IR ($CHCl_3$): ν = 3475 (OH), 1726, 1492, 1231, 1076, 1020, 756 cm^{-1}; HR-MS (ES): m/z = 336.1141, calcd. for $C_{18}H_{21}ClO_4$ $[M]^+$: 336.1128. *Tricycle* **19:** colorless oil; $[\alpha]_D$: +38.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.22 (dt, 1 H, *J* = 7.6, 1.5 Hz, Ar), 7.14 (t, 1 H, *J* = 8.0 Hz, Ar), 6.93 (td, 1 H, *J* = 7.5, 1.1 Hz, Ar), 6.80 (dd, 1 H, *J* = 8.2, 1.2 Hz, Ar), 5.93 (d, 1 H, *J* = 3.6 Hz, H1), 4.72 (m, 1 H, H2), 4.71 (m, 2 H, =CH_2), 4.65 (dd, 1 H, *J* = 3.9, 2.0 Hz, H4), 4.51 (d, 1 H, *J* = 1.6 Hz, H3), 3.85 (d, 1 H, *J* = 3.8 Hz, CH), 1.79 (t, 3 H, *J* = 3.1 Hz, Me), 1.57 (s, 3 H, Me), 1.36 (s, 3 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 209.0 (CO), 152.9, 128.9 (Ar, CH), 127.9 (Ar, CH), 121.1 (Ar, CH), 119.8, 116.3 (Ar, CH), 111.9, 105.2 (CH), 97.0, 83.3 (CH), 78.8 (CH), 75.7 (CH), 74.1 (=CH_2), 40.3 (CH), 26.6 (Me), 26.2 (Me), 16.5 (Me); IR ($CHCl_3$): ν = 2927, 1738 (CO), 1216, 1078, 1015, 757 cm^{-1}; HR-MS (ES): m/z = 316.1298, calcd. for $C_{18}H_{20}O_5$ $[M]^+$: 316.1311.

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[14] Experimental procedures as well as full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information. It contains as well copies of NMR spectra for all new compounds.

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Iron-catalyzed domino indole fluorination/allenic aza-Claisen rearrangement†

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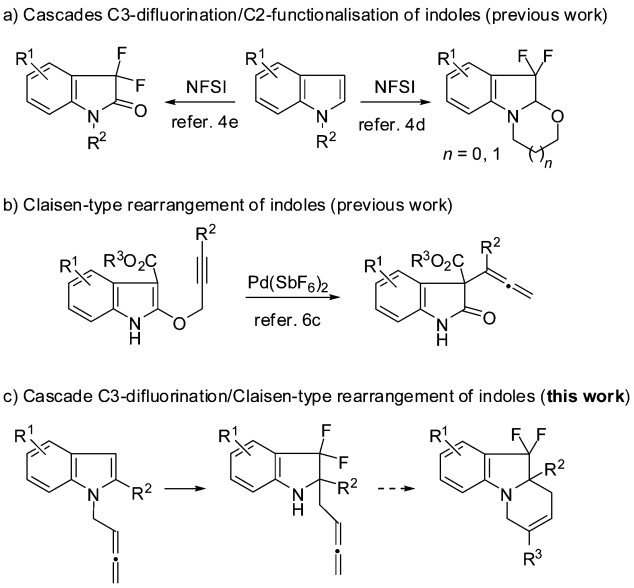
The synthesis of 2-allenyl-2-substituted-3,3-difluoroindolines has been accomplished, taking advantage of the reaction between *N*-allenyl-indoles and Selectfluor under iron catalysis.

Fluoroorganic molecules feature peculiar biological activities because of their improved lipophilicity and metabolic stability.[1] The difluoromethyl moiety is particularly relevant due to its isopolar and isosteric nature with $C(CH_3)_2$, C=O or hydroxyl groups.[2] On the other hand, the dearomatization of indoles has received considerable attention in organic synthesis because of the bioactivity of the resulting indolines.[3] Considerable efforts have been devoted to the fluorination of functionalised indoles [Scheme 1, eqn (1a)],[4] because this methodology is a direct entry to diverse fluorinated indoline structures. However, to the best of our knowledge, there is a lack of studies of the fluorofunctionalisation of the allenic indole moiety. This is rather surprising taking into account the rich chemistry of the allene moiety.[5]

As far as we know, the allene N1–C2 Claisen rearrangement of indoles has not been previously reported, with the C2–C3 Claisen rearrangement of indoles to form allenyl oxindoles being the only related precedent [Scheme 1, eqn (1b)].[6] We envisioned that allenic fluorinated indolines could be formed if a rearrangement step is associated with the fluorination sequence. This would be a highly valuable transformation because an additional allene moiety would be installed in the product serving as a platform for further functionalization. Considering the important properties of both polyfluorinated molecules as well as fused indolines, the β-amino 1,2-diene moiety of 2-allenyl-2-substituted-3,3-difluoroindolines may be a useful handle for cyclization reactions, and consequently for the achievement of difluorinated *N*-fused indolines. Herein we report an iron-catalyzed tandem process, namely, a fluorination/allenic aza-Claisen rearrangement[6] which forms 2-allenyl-2-substituted-3,3-difluoroindolines [Scheme 1, eqn (1c)].



Scheme 1 Indole as a platform for difluorination and allenic Claisen-type rearrangement: previous and current proposals.

Our initial efforts focused on the application of electrophilic fluorination to the selective construction of difluoroindolines with a quaternary center. Allenic indole **2a** was chosen as a model substrate for the fluorofunctionalisation reaction. Attempts to profitably generate a difluoroindoline structure from **2a** using Selectfluor without additives failed.[7] A more promising result was encountered through the addition of sodium bicarbonate, although more of the starting material remained unreacted. Also, 3,3-difluoroindoline **3a** was isolated along with a minor component, the unstable 3-fluoroindole **4a** (Scheme 2).

To mitigate the poor reactivity of allenylindole **2a** as well as the formation of intermediate **4a**, we intended the activation of the allene moiety through Lewis acid catalysis (Table 1). Initially, in order

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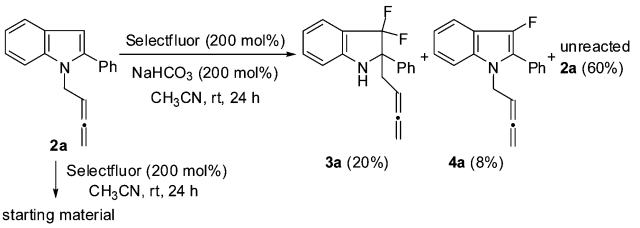
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data of new compounds, and copies of NMR spectra. See DOI: 10.1039/c6cc02012g



Scheme 2 Reaction of 1-allenyl-2-phenyl-indole **2a** with Selectfluor.

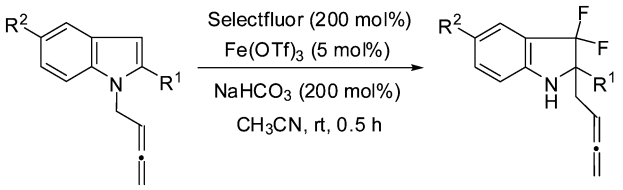
Table 1 Selective fluorination/rearrangement sequence of allenyl indole **2a** under modified metal-catalyzed conditions

Entry	Metallic salt	Yield[a] (%)
1	$[(Ph_3P)AuNTf_2]$	83
2	$PtCl_2$	71
3	$InCl_3$	63
4	$HfCl_4$	64
5	$Fe(OTf)_3$	81

[a] Yield of pure, isolated product with correct analytical and spectral data.

to get a better result in the formation of product **3a**, we attempted a gold-catalyzed reaction.[8] Fortunately, the addition of $[(Ph_3P)AuNTf_2]$ (5 mol%) allowed us to efficiently transform in just one hour substrate **2a** into 2-allenyl-2-phenyl-3,3-difluoroindoline **3a** in a totally selective fashion (Table 1, entry 1). It was interesting at this point to test the catalytic abilities of different metallic salts. The difluorination/rearrangement sequence could also be catalyzed by $PtCl_2$, $InCl_3$, and $HfCl_4$ but with slightly diminished effectiveness. Interestingly, the use of $Fe(OTf)_3$ gave similar results to Gagosz' catalyst (Table 1, entry 5). Taking into account the inexpensiveness and eco-friendliness of iron(III) salts, we decided to develop further the $Fe(OTf)_3$-catalyzed fluoro-rearrangement. When Selectfluor (200 mol%) was used as the fluorination reagent, the spots on the tin-layer chromatographic (TLC) plate of the reaction mixture looked very clean. However, alternative fluorine sources such as *N*-fluorobenzenesulfonimide afforded poorer results. Among all of the solvents examined, acetonitrile proved to be the best choice, affording product **3a** in a good 81% yield (Scheme 3). The metal-catalysed reaction between indole **2a** and Selectfluor in the absence of $NaHCO_3$ did not go to completion, thus highlighting the importance of the base for the success of the difluoroindoline formation.

To explore the effects of various substrates on fluorofunctionalisation reactions, a number of new indole-tethered allenes were synthesized. As shown in Scheme S1 (see ESI†), the starting materials, allenes **2a–m**, were made from the corresponding terminal alkynes **1a–m** by treatment with paraformaldehyde in the presence of diisopropylamine and copper(I) bromide (Crabbé reaction).[9]

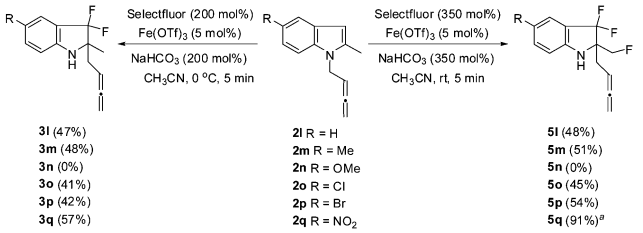


2a R^1 = Ph, R^2 = H	**3a** (83%)
2b R^1 = 4-ClC_6H_4, R^2 = H	**3b** (66%)
2c R^1 = 4-FC_6H_4, R^2 = H	**3c** (40%)
2d R^1 = 4-MeC_6H_4, R^2 = H	**3d** (48%)
2e R^1 = 4-*t*BuC_6H_4, R^2 = H	**3e** (43%)
2f R^1 = naphthalen-2-yl, R^2 = H	**3f** (55%)
2g R^1 = 4-MeC_6H_4, R^2 = Me	**3g** (52%)
2h R^1 = 4-MeC_6H_4, R^2 = OMe	**3h** (42%)
2i R^1 = 4-MeC_6H_4, R^2 = F	**3i** (44%)
2j R^1 = Ph, R^2 = NO_2	**3j** (92%)[a]
2k R^1 = Ph, R^2 = CN	**3k** (97%)[a]

Scheme 3 Synthesis of 2-aryl-2-(buta-2,3-dienyl)-3,3-difluoroindolines **3a–i**. [a] Chromatographic purification was not necessary.

With an optimized fluorofunctionalisation system in hand, we investigated the behaviour of 1-(buta-2,3-dienyl)-2-aryl-1*H*-indoles **2b–i**. As shown in Scheme 3, all 1-allenyl-2-aryl-substituted substrates exhibited excellent reactivity in the domino indole fluorination/allenic aza-Claisen rearrangement. The steric properties of the substituents in the indole moiety did not affect the reactivity significantly, with *tert*-butylphenyl and naphthalen-2-yl functionalized indoles **2e** and **2f** performing well in the formation of difluoroindolines **3e** and **3f**. Besides, it does not matter whether electron-withdrawing (such as 4-ClC_6H_4 and 4-FC_6H_4) or electron-donating groups (such as 4-MeC_6H_4) are introduced to the 2-aryl substituent as far as conversions are concerned. The presence of substituents at the benzene fused ring provided the same reactivity pattern independently of the electronic nature, such as in substrates **2g** and **h**, bearing EDG, or in substrates **2i–k**, bearing EWG. Taking into account all of the examples of Scheme 3, the reaction proved to be functional group tolerant. Complete conversion was observed by TLC and ^1H NMR analysis of the crude reaction mixtures of the indole-tethered allenes **2**, and no side-products were detected. Unfortunately, some decomposition was observed for the sensitive fluoroindolines **3** during purification using flash chromatography, which may be responsible for the moderate isolated yields. Nicely, using deactivated silica gel during chromatographic purification resulted in a detectable (5–10%) improvement in the isolated yields of products **3** and **5**. Even more interestingly, nitro- and cyano-derivatives **3j** and **3k** did not require further purification and were obtained in excellent yields.

Despite its usefulness, the catalytic C–F bond formation at sp^3 carbon centres using electrophilic reagents remains a synthetic challenge, because incorporation of fluorine into sp^3-hybridized carbons is achieved through nucleophilic fluorination reactions.[10] Originally, we were attempting the iron-catalysed difluoro-functionalisation/rearrangement sequence of *N*-allenylindole **2l** under Fe(III) catalysis (5 mol%) in the presence of Selectfluor (200 mol%). The expected product **3l** was the minor component, but, surprisingly, a 20% yield of the trifluoroindoline **5l** was obtained.



Scheme 4 Synthesis of 2-(buta-2,3-dienyl)-3,3-difluoro-2-methyl indolines **3** and 2-(buta-2,3-dienyl)-2-fluoromethyl-3,3-difluoroindolines **5**. [a] Chromatographic purification was not necessary.

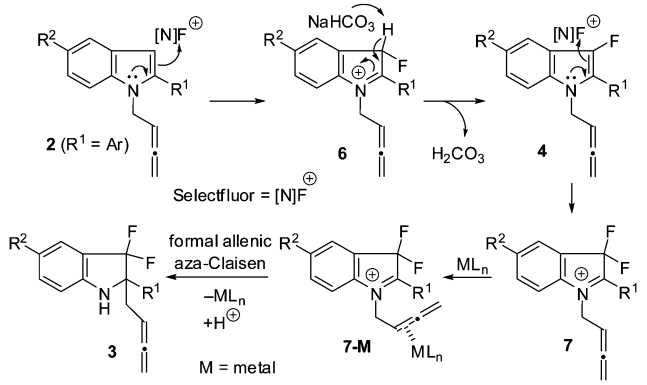
Consequently, our studies focused on developing a more efficient transformation. The reaction product **5l** could only be obtained in reasonable yield using a higher fluorination reagent loading. It is worthy of note that after considerable experimentation we were able to find suitable conditions for the controllable formation of both type of adducts, **3** and **5** (Scheme 4). 1-Allenyl-2-methyl-indoles **2** on exposure to the system $Fe(OTf)_3$ (5 mol%), $NaHCO_3$ (200 mol%), and Selectfluor (200 mol%) in acetonitrile at 0 °C, exclusively afforded 2-methyl-3,3-difluoroindolines **3** in just 5 minutes. By contrast, the reaction of substrates **2** with $Fe(OTf)_3$ (5 mol%), $NaHCO_3$ (350 mol%), and Selectfluor (350 mol%) in acetonitrile at room temperature did allow the sole formation of 2-fluoromethyl-3,3-difluoroindolines **5**. Unfortunately, compound **2n**, with a methoxy substituent at the C5 indole moiety, only led to several unidentified products upon treatment with Selectfluor. Nitro adduct **5q** did not require further purification and was obtained in nearly quantitative yield.

We monitored the reaction of *N*-allenylindole **2b** using both ^1H NMR and ^{19}F NMR spectroscopy in order to track the reaction intermediates (Fig. S1 and S2, see ESI†). Because of the paramagnetic character of $Fe(OTf)_3$ we selected $[(Ph_3P)AuNTf_2]$ as catalyst. Unfortunately, results were inconclusive. Although merely speculative at this time, the iron-catalysed generation of 2-(allenyl)-2-aryl-3,3-difluoroindolines **3** should proceed as outlined in Scheme 5. Accordingly, we initially propose a Selectfluor-assisted indole monofluorination to form 2-substituted-3-fluoroindoles **4** as represented by intermediate **6**. Taking into account that the reaction does not work without $NaHCO_3$, it may be safe to propose that $NaHCO_3$ should act as a base to facilitate the deprotonation of iminium species **8** to give the aromatic 3-fluoroindoles **4**.[11,12] After delivering the first fluorine atom, again Selectfluor attacks the indole C2–C3 double bond to form difluorospecies **7**. This attack occurs because of the stability of the resulting intermediate iminium cation **7**. Next, the metallic catalyst and **7** form metal-coordinate allene **7-M**, further inducing a formal allenic aza-Claisen rearrangement, which liberates 2-substituted-2-(buta-2,3-dienyl)-3,3-difluoroindolines **3** with concomitant regeneration of the catalytic species.

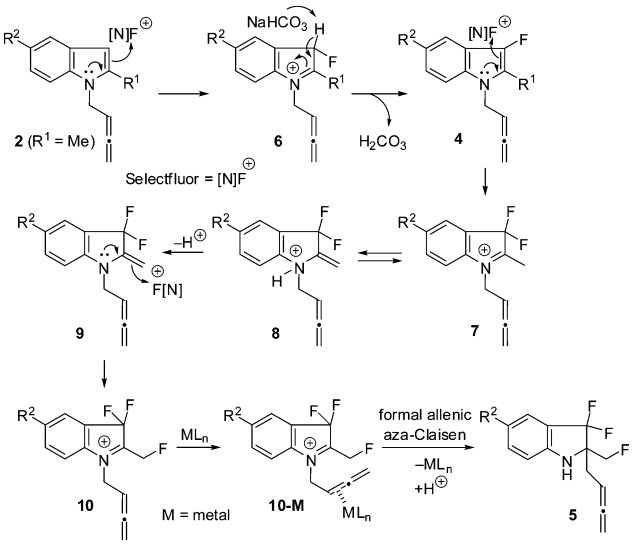
To investigate the reversibility of the fluorination/rearrangement process, 2-(allenyl)-2-phenyl-3,3-difluoroindoline **3a** was treated under metal-catalyzed conditions. Interestingly, it was found that 1-(buta-2,3-dienyl)-3-fluoro-2-phenyl-1*H*-indole **4a** was produced, which may point to a formal retro-allenic aza-Claisen rearrangement process, with the concomitant formation of 3-fluoro-2-phenyl-1*H*-indole, in which a N–C bond cleavage has occurred (Scheme S2, see ESI†). This outcome demonstrated that the fluorination/rearrangement sequence had a certain degree of reversibility under the promotion of $[(Ph_3P)AuNTf_2]$ or $Fe(OTf)_3$.

A related pathway for the iron-catalysed generation of 2-(allenyl)-2-fluoromethyl-3,3-difluoroindolines **5** is outlined in Scheme 6. A similar scenario to the first and second fluorination can be postulated for the third fluorination, through the attack of Selectfluor to the enamine double bond of **9** to form iminium species **10**. Thus, whereas the 1-(allenyl)-2-aryl-1*H*-indoles exclusively lead to 2-aryl-3,3-difluoroindoline adducts **3**, the 2-methyl counterparts produce 2-fluoromethyl-3,3-difluoroindoline products **5**.

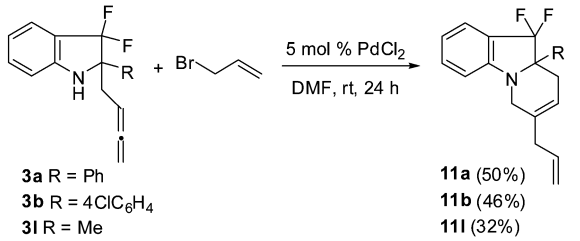
N-Fused indolines are widely spread natural products which exhibit relevant biological properties.[13,14] Owing to the efficacy and functional group tolerance of transition metal catalyzed coupling reactions in forming C–heteroatom bonds starting from allenes, we envisioned that our 2-allenyl-3,3-difluoroindolines may be synthetically interesting building blocks for the preparation of *N*-fused indoline derivatives. The carbocyclization–functionalisation



Scheme 5 Tentative mechanistic explanation for the Selectfluor-promoted metal-catalyzed synthesis of 2-(allenyl)-2-aryl-3,3-difluoroindolines **3**.



Scheme 6 Tentative mechanistic explanation for the Selectfluor-promoted metal-catalyzed synthesis of 2-(allenyl)-2-fluoromethyl-3,3-difluoroindolines **5**.



Scheme 7 Synthesis of 10,10-difluoro-tetrahydropyrido[1,2-*a*]indoles **11** and **12**.

of the aminoallene subunit was realized when allyl bromide was added in the palladium-catalyzed transformation of 2-allenyl-1*H*-indoles **3** to generate *N*-fused indolines **11** (Scheme 7).

In conclusion, an efficient iron-catalyzed Selectfluor-assisted synthetic route to 2-allenyl-2-substituted-3,3-difluoroindolines from easily accessible *N*-allenyl-indole substrates under mild conditions has been reported. The Fe(III)/Selectfluor system enables the highly selective difluorofunctionalisation/aza-Claisen rearrangement sequence of various 1-allenyl-2-aryl-indoles at ambient temperature. Besides, trifluoroderivatives can be achieved starting from 1-allenyl-2-methyl substrates. Future work could be directed towards the development of an asymmetric version.

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11 Although the isolation of 1-(buta-2,3-dienyl)-3-fluoro-2-phenyl-1*H*-indole **4a** from the uncatalyzed reaction of **2a** outlined in Scheme 2 was fortuitous, some information has been gathered in favor of the pathway shown in Scheme 6.

12 In order to see if compound **4a** is able to rearrange to **3a** under metal catalysis, reaction of **4a** with a catalytic amount of either $Fe(OTf)_3$ or $[(Ph_3P)AuNTf_2]$ was conducted in the presence of Selectfluor and $NaHCO_3$. The reaction did proceed well to give 3,3-difluoroindoline **3a**. Therefore, we have enough evidence to propose that 3-fluoroindole **4a** is indeed an intermediate.

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Catalysis

Metal-Catalyzed Cyclization Reactions of 2,3,4-Trien-1-ols: A Joint Experimental–Computational Study

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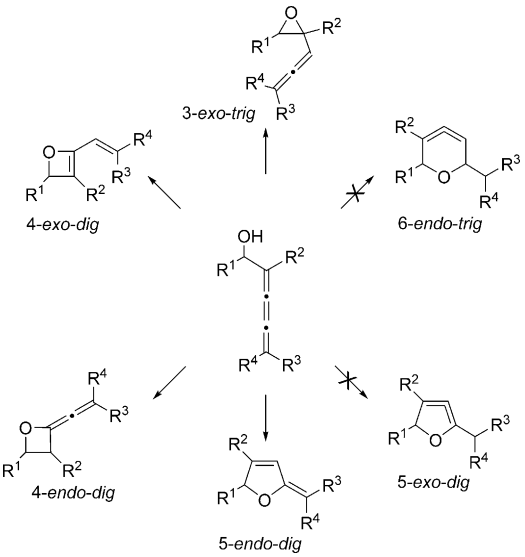
Abstract: Controlled preparation of tri- and tetrasubstituted furans, as well as carbazoles has been achieved through chemo- and regioselective metal-catalyzed cyclization reactions of cumulenic alcohols. The gold- and palladium-catalyzed cycloisomerization reactions of cumulenols, including indole-tethered 2,3,4-trien-1-ols, to trisubstituted furans was effective, due to a 5-*endo-dig* oxycyclization by attack of the hydroxy group onto the central cumulene double bond. In contrast, palladium-catalyzed heterocyclization/coupling reactions with 3-bromoprop-1-enes furnished tetrasubstituted furans. Also studied was the palladium-catalyzed cyclization/coupling sequence involving protected indole-tethered 2,3,4-trien-1-ols and 3-bromoprop-1-enes that exclusively generated trisubstituted carbazole derivatives. These results could be explained through a selective 6-*endo-dig* cumulenic hydroarylation, followed by aromatization. DFT calculations were carried out to understand this difference in reactivity.

Introduction

Among different strategies to build up heterocycles, cycloisomerization reactions have been studied in great detail from both synthetic and theoretical standpoints. Particularly, the catalytic intramolecular addition of a pendant nucleophile group to a cumulene functionality can be viewed as a highly efficient and atom-economical synthetic strategy. Among cumulene derivatives, 2,3-dien-1-ols are well-studied,[1] whereas similar reactions for 2,3,4-trien-1-ols are unfamiliar.[2] This lack of reports is probably associated with several drawbacks such as 1) difficult-to-prepare starting materials, and 2) difficulties in controlling selectivity to get the desired adducts over undesired isomers.

Oxacyclic structures, such as furan derivatives, are found in numerous biologically active natural products.[3] Potentially, a metal-catalyzed heterocyclization reaction of α-cumulenols would produce different three-, four-, five-, or six-membered oxacycles. Depending on the regioselectivity (3-*exo-trig* vs. 4-*exo-dig* vs. 4-*endo-dig* vs. 5-*endo-dig* vs. 5-*exo-dig* vs. 6-*endo-trig* cyclization modes) any of the six possible cycloisomerization adducts could be the reaction products (Scheme 1). However, bent cyclic allene adducts derived from 5-*exo-dig* and 6-*endo-trig* attacks are too constrained to be formed.[4] As a continuation of our study in this field, we decided to examine the influence of different metal activators on the cycloetherification reaction of 2,3,4-trien-1-ols, aiming for different reaction modes that can be realized in a controllable manner.



Scheme 1. General scheme defining the cycloisomerizations that can take place involving α-cumulenols.

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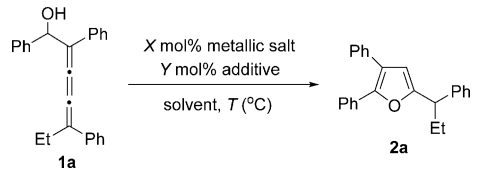
Supporting information and ORCIDs from the authors for this article are available on the WWW under http://dx.doi.org/10.1002/chem.201601838. It contains compound characterization data, experimental procedures, Cartesian coordinates, and copies of NMR spectra for all new compounds.

Results and Discussion

The synthesis of oxycyclization precursors, 2,3,4-trien-1-ols **1a–e**, was accomplished by a zirconium-mediated coupling reaction of 1,3-butadiynes with aldehydes using previously described methods.[5] To explore the effects of various complexes on the metal-catalyzed heterocyclization reaction of 2,3,4-trien-1-ols, α-cumulenol **1a** was selected as a model substrate. Initially, it was hoped that a catalytic activation strategy could be developed through the use of noble-metal salts.[6,7] Experiments were carried out with 2,3,4-trien-1-ol **1a** using different catalysts, and changing catalyst loadings, solvents, and temperatures (see Table 1). The cyclization reaction was optimized by systematically changing several reaction parameters. Lower yields were observed when using halogenated solvents such as dichloromethane and 1,2-dichloroethane. Among all the solvents examined, DMF and toluene proved to be the best choices and performing the reaction in refluxing toluene gave the best results. Unfortunately, all attempts to carry out the ring closure using platinum-based catalysis failed: decomposition products were detected in the reaction mixture after 12 h irrespective of conditions used (Table 1, entries 1–3). Among the tested gold(I) salts, Gagosz' catalyst was the most suitable promoter (entry 8). Because palladium compounds are very efficient in a variety of catalytic organic transformations,[8] we next decided to use palladium catalysis. Notably, palladium complexes proved to be a good alternative to the expensive Gagosz' catalyst. Finally, the optimal palladium-catalyzed reaction conditions for the formation of furan **2a** turned out to be $Pd(OAc)_2$ in the presence of triphenylphosphine in refluxing toluene (entry 14). Thus, furan **2a** could be isolated after purification by column chromatography in 80% yield after $Pd(OAc)_2$ treatment. Remarkably, no water elimination was observed, indicating that this potentially serious side reaction failed to proceed at a significant rate under the above Pd-catalyzed conditions.[9] The catalyst loading was reduced to 3% without a considerable decrease of the reaction yield (entry 15). Further reduction of the catalyst loading to 1 mol% resulted in a reaction mixture that included appreciable amounts of unreacted starting material (entry 16).

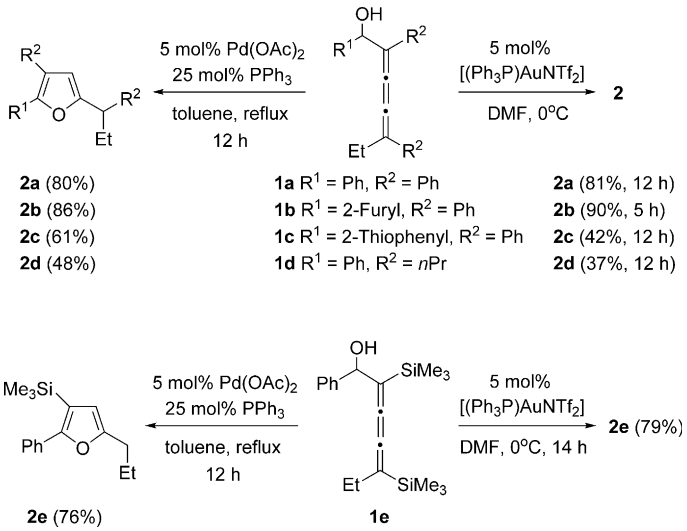
Table 1. Selective oxycyclization reaction of 2,3,4-trien-1-ol **1a** under modified metal-catalyzed conditions.[a]



Entry	Metallic salt (mol%)	Additive (mol%)	Solvent/T [°C]	Yield [%][b]
1	$PtCl_2$ (1)	–	DMF/20	–
2	$PtCl_2$ (5)	AgOTf (1)	DMF/20	–
3	$[PtCl_2(CH_2{=}CH_2)]_2$ (5)	TDMPP (10)	DMF/20	–
4	[IPrAuCl] (5)	$AgSbF_6$ (5)	CH_2Cl_2/20	52
5	[IPrAuCl] (5)	$AgSbF_6$ (5)	DMF/20	57
6	$[(Ph_3P)AuNTf_2]$ (5)	–	CH_2Cl_2/20	60
7	$[(Ph_3P)AuNTf_2]$ (5)	–	DMF/20	72
8	$[(Ph_3P)AuNTf_2]$ (5)	–	DMF/0	81
9	$[(Ph_3P)AuNTf_2]$ (5)	–	toluene/20	65
10	$PdCl_2$ (5)	–	toluene/20	37
11	$Pd(OAc)_2$ (5)	–	DMF/20	71
12	$Pd(OAc)_2$ (5)	–	toluene/20	43
13	$Pd(OAc)_2$ (5)	–	toluene/110	49
14	$Pd(OAc)_2$ (5)	PPh_3 (25)	toluene/110	80
15	$Pd(OAc)_2$ (3)	PPh_3 (25)	toluene/110	76
16	$Pd(OAc)_2$ (1)	PPh_3 (25)	toluene/110	48
17	$Pd(PPh_3)_4$ (5)	–	toluene/110	37

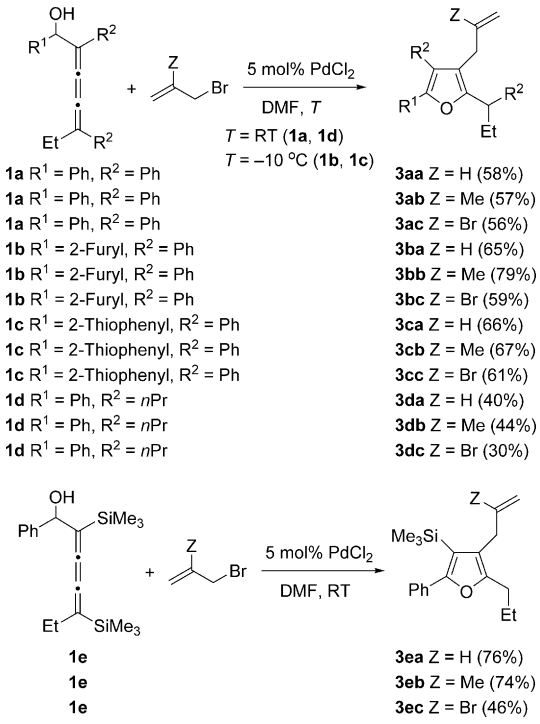
[a] DMF = *N*,*N*-dimethylformamide. TDMPP = tris(2,6-dimethoxyphenyl)-phosphine. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [b] Yield of pure, isolated product with correct analytical and spectral data.

Having found the optimal reaction conditions, the scope of the oxycyclization reaction was explored using differently substituted cumulative allenols. A variety of 2,3,4-trien-1-ol derivatives **1a–e** underwent a smooth Pd-catalyzed cycloisomerization to afford the corresponding trisubstituted furan products **2a–e** (Scheme 2). These examples show that both aliphatic and aromatic substituents are well tolerated. The trimethylsilyl group linked to the aliphatic substituent in the furan adduct resulting from the cycloisomerization reaction of 2,3,4-trien-1-ol **1e** was cleaved under the mild acidic conditions of the metal-catalyzed reaction media.



Scheme 2. Metal-catalyzed cycloisomerization of 2,3,4-trien-1-ols **1**. Preparation of trisubstituted furans **2**.

To find out whether cumulenols **1** are useful precursors not only for cycloisomerization, but also for cyclization/functionalization reactions, a different reactivity in the presence of a coupling partner was tested. The cyclization/functionalization of 2,3,4-trien-1-ols **1** was attempted using our previously optimized protocol for 2,3-dien-1-ols.[10d] In a preliminary experiment, 2,3,4-trien-1-ol **1a** was treated with allyl bromide in the presence of 5 mol% $PdCl_2$ in DMF. To our delight, the cyclization/cross-coupling reaction proceeded smoothly at room temperature to afford the corresponding tetrasubstituted furan **3aa** in 58% yield (Scheme 3). Notably, oxycyclization/functionalization of the α-cumulenol subunit could be achieved when



Scheme 3. Palladium-catalyzed oxycyclization/functionalization of 2,3,4-trien-1-ols **1**. Preparation of tetrasubstituted furans **3**.

allyl bromide was added to the palladium-catalyzed reaction. Inspired by this result, we extended this reaction sequence to various α-cumulenols **1b–e** (Scheme 3). It was found that tetrafunctionalized furans were obtained through this heterocyclization/coupling sequence by readily adjusting the reaction temperature. Thus, the optimal reaction conditions for cumulenols **1b** and **1c** were finally established as a reaction temperature of −10 °C. The scope of this tandem Pd-catalyzed reaction was further exemplified by the coupling of both 3-bromo-2-methylprop-1-ene and 2,3-dibromoprop-1-ene with different 2,3,4-trien-1-ols (Scheme 3). In most cases, the corresponding adducts **3aa–ec** were obtained in reasonable yields. Interestingly, the heterocyclization/cross-coupling sequence of 2,3,4-trien-1-ol **1e** bearing two sensitive TMS groups gave rise to furans **3ea–ec**, in which only the trimethylsilyl moiety directly attached to the heterocycle was retained.

DFT calculations were carried out to gain more insight into the exclusive formation of furans **2** and the reaction mechanism involved in the subsequent coupling reaction with allyl bromides leading to furans **3**.

To this end, we first explored the different cyclization reactions from the initial intermediates **A**, **B**, and **C** formed upon coordination of the $PdCl_2$ catalyst to the different C=C double bonds of the model 2,3,4-trien-1-ol **1M**. From the data gathered in Figure 1, which shows the computed relative free energies (ΔG, at 298 K) in the presence of toluene as the solvent, it becomes clear that among the different cyclization modes, the 5-*endo-trig* cyclization is strongly favored under both thermodynamic and kinetic control. Moreover, the low computed activation barrier for this transformation ($\Delta G^{\neq} = 9.8$ kcal mol^{-1}) is compatible with a process occurring at room temperature as experimentally observed (see entry 10, Table 1).

Figure 2 shows the reaction profiles (using DMF as solvent in the calculations) for the evolution of the zwitterionic intermediate **INT1**, the species formed through the 5-*endo-trig* cyclization reaction, into the observed furans **2** and **3**, that is, the reaction products when the process is carried out in the absence or presence of allyl bromide, respectively.

Once the regioselective 5-*endo-dig* cumulenic oxypalladation has occurred, intermediate **INT1** evolves to neutral dihydrofuran **INT2** by the exergonic loss of HCl ($\Delta G_R = -4.8$ kcal mol^{-1}). Subsequent protonolysis of the C–Pd bond via transition-state **TS2** leads to **INT3**, a π-complex formed by coordination of the endocyclic C=C double bond to the palladium catalyst. The ease of this reaction step is clearly reflected in the rather low activation barrier ($\Delta G^{\neq} = 3.2$ kcal mol^{-1}) and high exergonicity ($\Delta G_R = -20.6$ kcal mol^{-1}) computed for this transformation. Final release of the $PdCl_2$ catalyst leads to **INT4** that after isomerization produces the observed furan **2M**. The high exergonicity computed for this isomerization reaction ($\Delta G_R = -15.3$ kcal mol^{-1}) is directly related to the aromatization of the five-membered ring that therefore constitutes the driving force of the transformation.

Alternatively, in the presence of allyl bromide, **INT2** may evolve into **INT5** by the exergonic coordination of the allylic C=C double bond to the unsaturated transition-metal fragment ($\Delta G_R = -12.0$ kcal mol^{-1}). A subsequent insertion reaction leads to **INT6**, a new π-complex formed upon coordination of

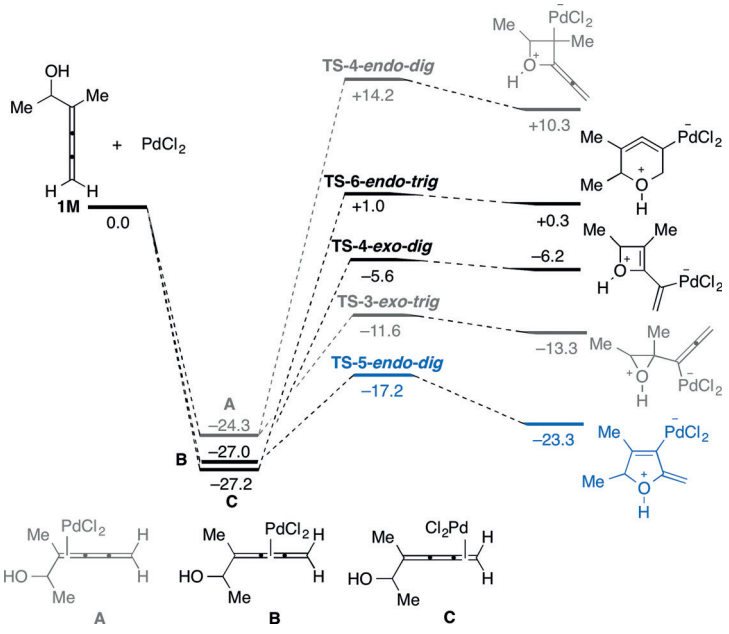


Figure 1. Computed possible cyclization modes for the reaction between 2,3,4-trien-1-ol **1M** and $PdCl_2$. Relative free energies (ΔG, at 298 K) are given in kcal mol^{-1}. All data have been computed at the PCM(toluene)-B3LYP-D3/def2-SVP level.

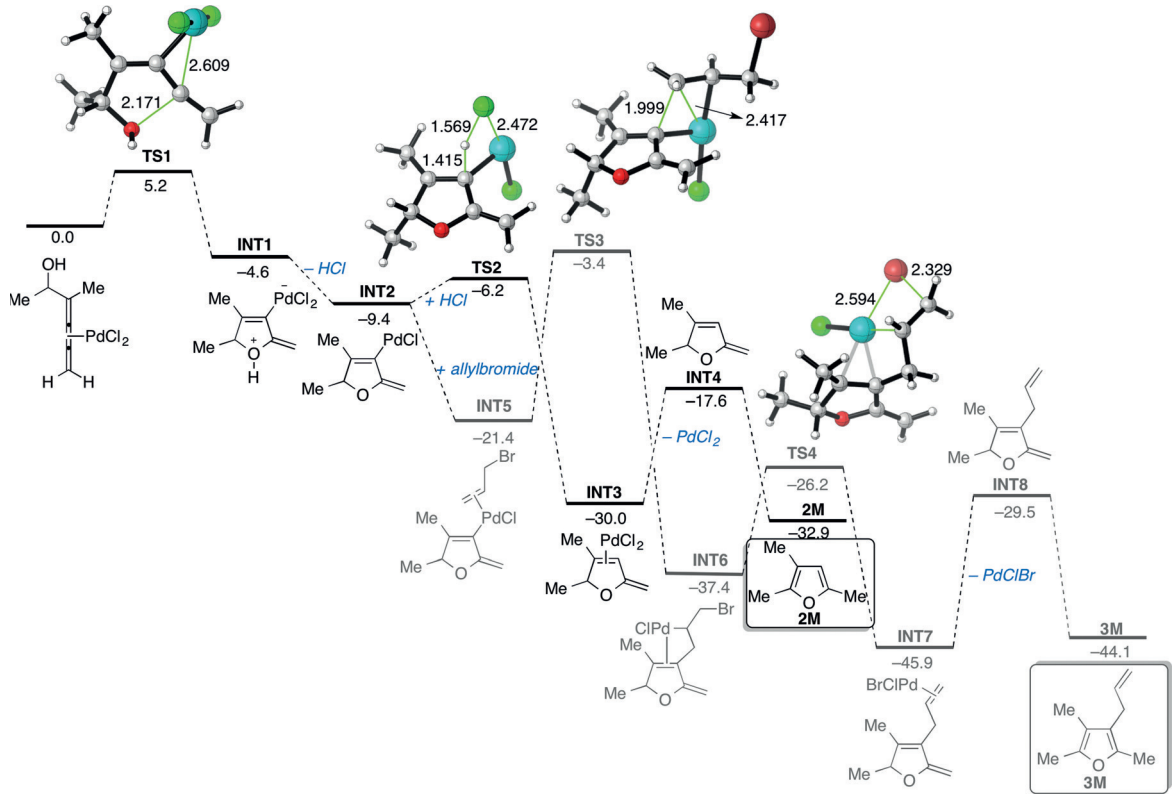
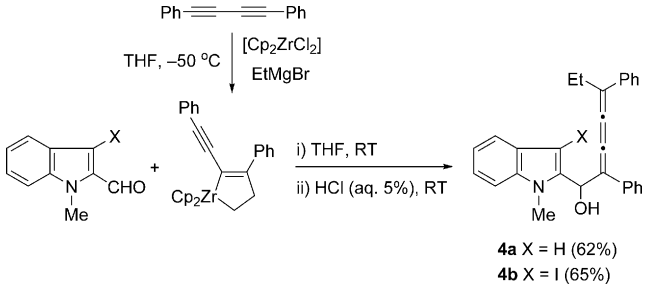


Figure 2. Computed reaction profiles for the transformation of **INT1** into furans **2M** and **3M**. Relative free energies (ΔG, at 298 K) and bond lengths are given in kcal mol^{-1} and angstroms, respectively. All data have been computed at the PCM(DMF)-B3LYP-D3/def2-SVP level.

the endocyclic C=C bond to the palladium moiety. This exergonic insertion reaction ($\Delta G_R = -16.0$ kcal mol^{-1}) proceeds through **TS3**, a saddle point associated with the formation of the new C–C bond ($\Delta G^{\neq} = 18.0$ kcal mol^{-1}). Then, a *trans* β-bromide elimination affords the coupling adduct, 2,5-dihydrofuran **INT7**, via **TS4**, a saddle point associated with the concomitant C–Br bond rupture/Pd–Br bond formation ($\Delta G^{\neq} =$ 11.2 kcal mol^{-1}, $\Delta G_R = -8.5$ kcal mol^{-1}). Similar to the process leading to furans **2**, final release of the PdClBr leads to **INT8**, which produces the observed furan **3M** after isomerization.

As indoles are integral parts of a variety of natural products, it would be of interest to subject cumulenyl indoles for the above metal-catalyzed conditions. We optimized the procedure for the preparation of novel indole-tethered 2,3,4-trien-1-ols **4** from 1,4-diphenylbuta-1,3-diyne and indole-2-carbaldehydes, such as 1-methyl-1*H*-indole-2-carbaldehyde and 3-iodo-1-methyl-1*H*-indole-2-carbaldehyde. Rewardingly, the zirconium-mediated coupling reactions proceeded smoothly over 12 h at room temperature to afford 2,3,4-trien-1-ols **4a** and **4b** in fair yields as single regioisomers after purification in deactivated silica gel (Scheme 4).

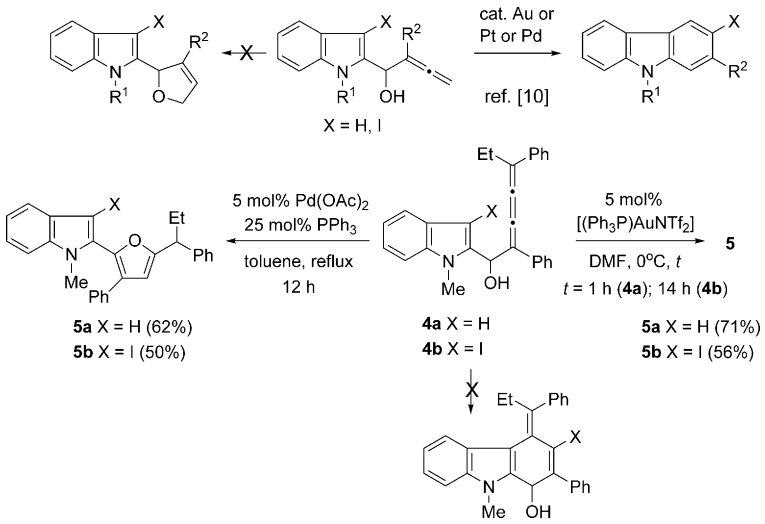
An interesting case of selectivity arises in 2,3,4-trien-1-ols **4**, because two potentially reactive moieties, namely, alcohol and indole, are present in the same substrate. In principle, two different cyclizations (O- or C-) can take place. Gratifyingly, it was observed that the metal-catalyzed reaction conditions using 2,3,4-trien-1-ols **1** were compatible with substrates **4**, resulting in the formation of the desired attached-ring indole-furans **5** in



Scheme 4. Zirconium-mediated synthesis of indole-tethered 2,3,4-trien-1-ols **4**.

fair yields with complete regio- and chemoselectivity (Scheme 5). It is noteworthy that the product distribution can be completely switched in comparison with related allenyl-indoles, for which the carbocyclization reaction is observed exclusively (Scheme 5).[10]

The gold(I)-catalyzed preferred formation of indole-linked furans **5** over the corresponding carbocyclization products was computationally explored as well. Figure 3 shows the computed reaction profiles for the competitive O- versus C-cyclization reactions. Our calculations suggest that the process begins with the initial coordination of the model $[AuPMe_3]^+$ catalyst to the central C=C double bond of the 2,3,4-trien-1-ol **4M** to afford the π-complex **INT8**. From this intermediate, the two possible cyclization reactions may occur. From the data in Figure 3, it becomes clear that the observed chemoselectivity



Scheme 5. Metal-catalyzed cycloisomerization of indole-tethered 2,3,4-trien-1-ols **4**. Preparation of indole-linked furans **5**.

takes place under kinetic control despite the higher exergonicity computed for the C-carbocyclization reaction ($\Delta\Delta G_R =$ 17.2 kcal mol^{-1}). The computed activation-barrier difference ($\Delta\Delta G^{\neq} = 2.4$ kcal mol^{-1}) is translated into a 99:1 (O- vs. C-) ratio, which agrees nicely with the experimental findings. Once the cationic complex **INT9-O** is formed, a highly exergonic ($\Delta G_R = -19.8$ kcal mol^{-1}) deprotonation reaction mediated by the NTf_2^- base occurs to produce neutral intermediate **INT10-O**. Subsequent protonolysis of the Au–C carbon by the readily formed $NHTf_2$ produces **INT11-O** following a reaction mechanism similar to that reported by us for strongly related transformations.[11] Once again, final decoordination of the metal fragment releases the catalyst and produces dihydrofuran **INT12-O**, which after isomerization affords the observed furan **5M**.

In the next experiment, the palladium-catalyzed reaction between indole-tethered 2,3,4-trien-1-ols **4** and 3-bromoprop-1-enes was studied. The reaction of indole-tethered cumulenols **4** proved to be as efficient as the reaction of more simple cumulenols **1**. The oxycyclization/functionalization sequence proceeded smoothly, selectively affording furan linked-indoles **6aa–bc** (Scheme 6). However, the 2,3,4-trien-1-ol **4a** when treated with allyl bromide afforded furan **6aa** as major component along with a minor product, the carbazole **7aa** (Scheme 6). Although the chemoselectivity (oxycyclization vs. carbocyclization) was no total in this particular case, isomers **6aa** and **7aa** were easily separated.

Carbazoles are an important class of heterocyclic scaffolds that exist widely in nature with interesting biological proper-

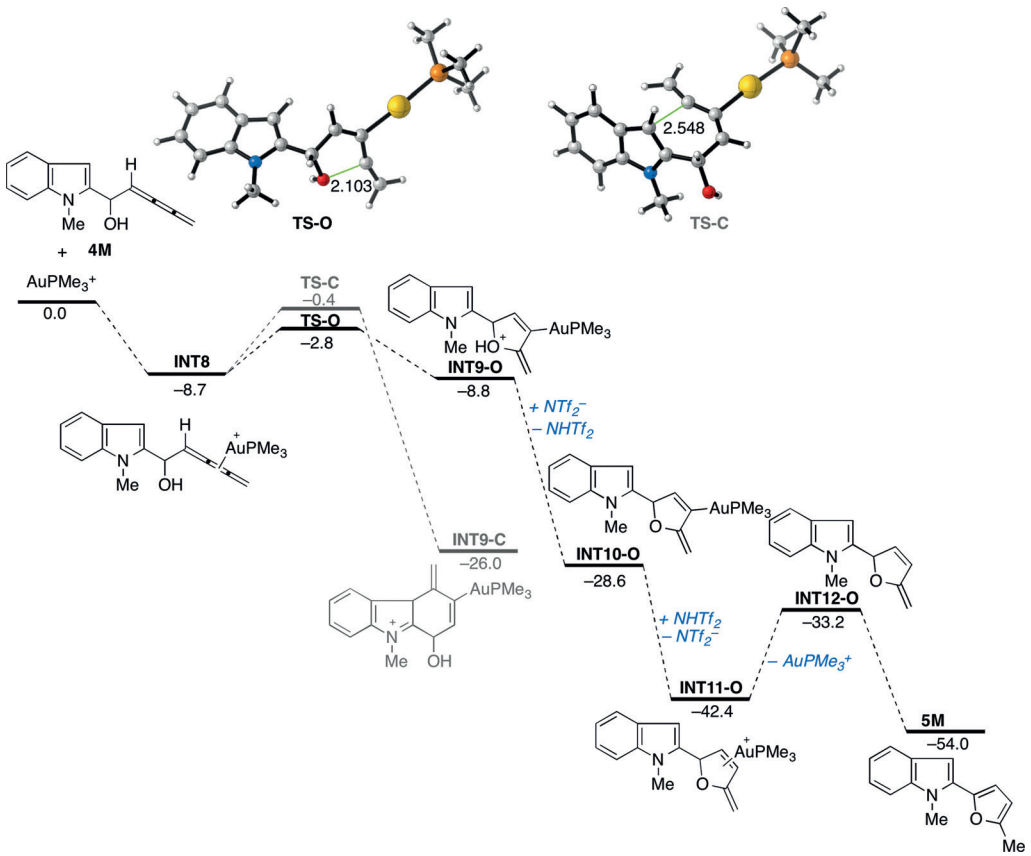
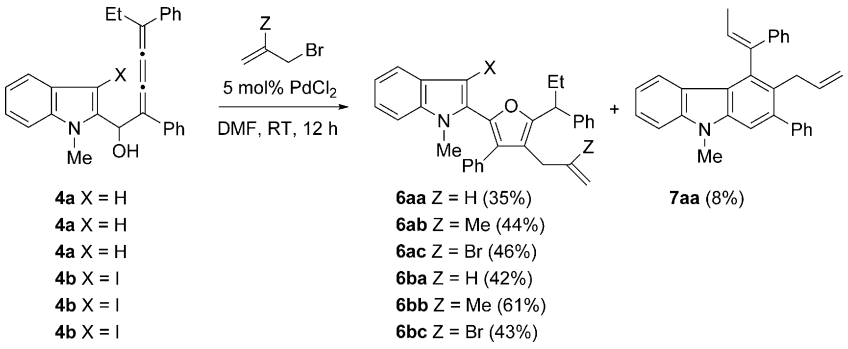
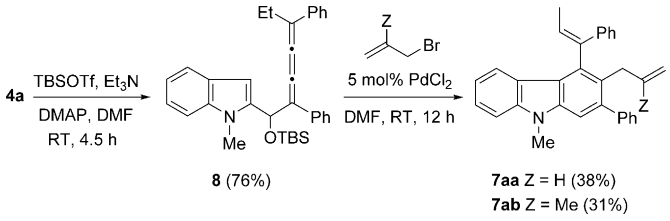


Figure 3. Computed reaction profiles for the transformation of indol **4**M into indole-linked furan **5**M. Relative free energies (ΔG, at 298 K) and bond lengths are given in kcal mol^{-1} and angstroms, respectively. All data have been computed at the PCM(DMF)-B3LYP-D3/def2-SVP level.



Scheme 6. Palladium-catalyzed oxycyclization/functionalization of indole-tethered 2,3,4-trien-1-ols **4**. Preparation of tetrasubstituted indole-linked furans **6**.

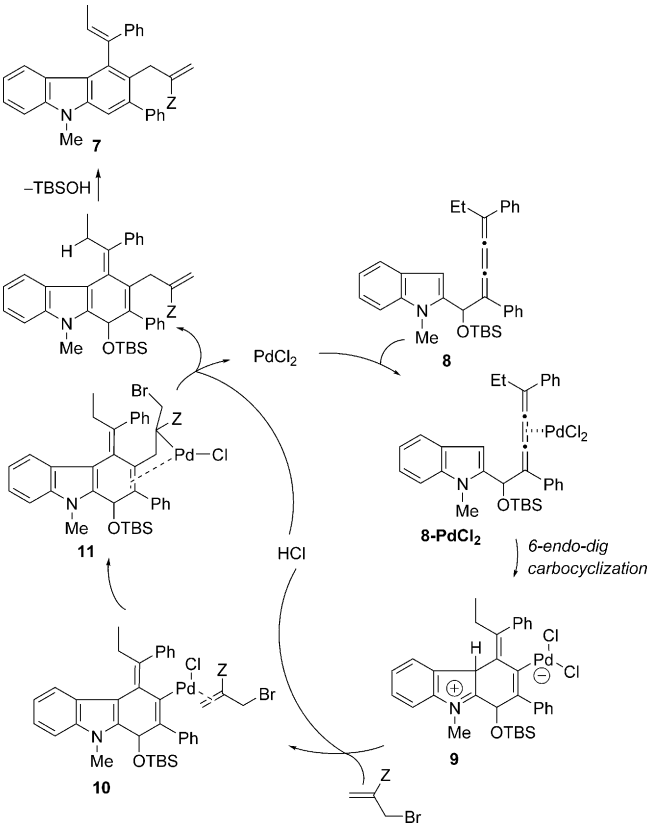
ties.[12] Moreover, the carbazole nucleus serves as a key molecular motif in materials science.[13] Development of effective methods for the construction of fuctionalized carbazoles is thus important in organic synthesis. Consequently, we decided to perform a switchable synthesis of different heterocycles, namely indole versus furan, from the same starting 2,3,4-trien-1-ol. To block the favored cycloetherification path, we utilized the OTBS derivative **8**, which was conveniently prepared using a standard protection protocol (Scheme 7). This silyl protection should force the otherwise unfavorable hydroarylation route



Scheme 7. Palladium-catalyzed carbocyclization/functionalization of indole-tethered (2,3,4-trien-1-yloxy)silane **8**. Preparation of trisubstituted carbazoles **7**. TBS = *tert*-butyldimethylsilyl.

and make the benzannulation feasible. To check this hypothesis, (2,3,4-trien-1-yloxy)silane derivative **8** was reacted with both allyl bromide and 3-bromo-2-methylprop-1-ene under otherwise identical palladium-catalyzed conditions. To our delight, the formation of furan adducts was suppressed, according to ^{1}H NMR analysis of the crude products. As shown in Scheme 7, the carbocyclization/coupling sequence took place to afford 2,3,4-trisubstituted carbazoles **7aa** and **7ab**. Unfortunately, some decomposition was observed on sensitive alkenylcarbazoles **7** during purification by flash chromatography, which may be responsible for the moderate isolated yields. A point to note is that the use of the indole-tethered protected 2,3,4-trien-1-ol moiety changes the reactivity pattern, overcoming the oxycyclization although retaining the same regioselectivity of the cyclization step. These results could be explained through a 6-*endo-dig* hydroarylation with concomitant dehydration (see below).

According to the reaction profiles discussed above (Figures 2 and 3), the following mechanism for the observed Pd-catalyzed benzannulation-functionalization of indolyl (2,3,4-trien-1-yloxy)-silane derivatives **8** to form carbazoles could be proposed (Scheme 8). Initial Pd-coordination to the 2,3,4-triene moiety would produce a cumulene–palladium complex **8**–$PdCl_2$. Species **8**–$PdCl_2$ would then undergo an intramolecular chemo- and regioselective 6-*endo-dig* carbocyclization reaction to give the zwitterionic intermediate palladadihydrocarbazole **9**, which may react with the 3-bromoprop-1-ene derivative via **10** to form intermediate **11**. A *trans* β-heteroatom elimination with concurrent *tert*-butyldimethylsilanol release under the reaction conditions generates carbazoles of type **7** with concomitant regeneration of the palladium catalyst (Scheme 8).



Scheme 8. Mechanistic explanation for the palladium-catalyzed carbocyclization/functionalization of indole-tethered 2,3,4-triene **8**.

Conclusions

In conclusion, the controlled preparation of tri- and tetrasubstituted furans, as well as carbazoles has been achieved through chemo- and regioselective metal-catalyzed cyclization reactions of cumulenic alcohols. Chemo- and regiocontrol issues are influenced neither by the nature of the tether or the metal catalyst. Computational investigations allow the rationalization of this reactivity.

Experimental Section

Computational details

All the calculations reported in this paper were performed with the Gaussian 09 suite of programs.[14] Electron correlation was partially taken into account using the hybrid functional usually denoted as B3LYP[15] in conjunction with the D3 dispersion correction suggested by Grimme et al.[16] using the double-ζ quality plus polarization def2-SVP[17] basis set for all atoms. Reactants and products were characterized by frequency calculations,[18] and have positive definite Hessian matrices. Transition structures (TS's) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the Intrinsic Reaction Coordinate (IRC) method.[19] Solvents effects were taken into account using the Polarizable Continuum Model (PCM)[20] during the geometry optimizations. This level is denoted PCM-(solvent)-B3LYP-D3/def2-SVP.

General methods

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, Bruker Avance-300 or Varian VRX-300S. NMR spectra were recorded in $CDCl_3$ solutions, except when otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, $\delta=$ 0.00 ppm), or $CDCl_3$ (^{1}H, $\delta=7.27$ ppm; ^{13}C, $\delta=76.9$ ppm), or [D$_6$]acetone (^{1}H, $\delta=2.0$ ppm; ^{13}C, $\delta=206.3$ ppm), or C_6D_6 (^{1}H, $\delta=$ 7.16 ppm; ^{13}C, $\delta=128.0$ ppm). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. All commercially available compounds were used without further purification.

General procedure for the Pd^{II}-catalyzed cycloisomerization of 2,3,4-trien-1-ols 1 and 4

Preparation of trisubstituted furans 2 and 5: Method A

$Pd(OAc)_2$ (0.05 mmol) and (Ph_3P) (0.25 mmol) were sequentially added to a stirred solution of the appropriate 2,3,4-trien-1-ol **1** or **4** (1.0 mmol) in toluene (10 mL) under argon. The resulting mixture was stirred at reflux until disappearance of the starting material was observed (TLC, typically 12 h). The reaction mixture was allowed to cool to room temperature and it was filtered through a pad of Celite. The reaction was then quenched with brine (1.0 mL) and the mixture was extracted with ethyl acetate (3× 10 mL). The combined extracts were washed twice with brine and dried ($MgSO_4$). The solution was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave adducts **2** or **5**. Spectroscopic and analytical data for pure forms of **2** or **5** follow.[21]

General procedure for the Au^{I}-catalyzed cycloisomerization of 2,3,4-trien-1-ols 1 and 4

Preparation of trisubstituted furans 2 and 5: Method B

[(Ph_3P)AuNTf$_2$] (0.05 mmol) was added to a stirred solution of the appropriate 2,3,4-trien-1-ol **1** or **4** (1.0 mmol) in *N*,*N*-dimethylformamide (10 mL) at 0 °C under argon. The resulting mixture was stirred at 0 °C until disappearance of the starting material was observed (TLC, 1–14 h). The reaction mixture was filtered through a pad of Celite. Water (5 mL) was added to the filtrate before being extracted with ethyl acetate (3×10 mL). The combined extracts were washed twice with brine and dried ($MgSO_4$). The solution was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave adducts **2** or **5**. Spectroscopic and analytical data for pure forms of **2** or **5** follow.

3-Phenyl-5-(1-phenylpropyl)-2,2′-bifuran 2b: From 86 mg (0.30 mmol) of 2,3,4-trien-1-ol **1b**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as the eluent, compound **2b** (85 mg, 86%, method A; 89 mg, 90%, method B) was produced as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=$ 7.40 (dd, 2H, $J=8.5$, 1.5 Hz, Ar), 7.26 (m, 9H, Ar), 6.37 (dd, 1H, $J=$ 3.5, 0.7 Hz, Ar), 6.31 (dd, 1H, $J=3.4$, 1.8 Hz, Ar), 6.13 (d, 1H, $J=$ 0.7 Hz, Ar), 3.81 (t, 1H, $J=7.6$ Hz, CH), 2.15 (m, 1H, $J=7.2$ Hz, C*H*H), 1.89 (m, 1H, $J=7.2$ Hz, CH*H*), 0.88 ppm (t, 3H, $J=7.3$ Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=$ 157.8, 146.4, 142.2, 141.6 (Ar, CH), 139.6, 133.5, 128.5 (Ar, 4CH), 128.3 (Ar, 2CH), 128.0 (Ar, 2CH), 127.1 (Ar, CH), 126.6 (Ar, CH), 123.2, 111.1 (Ar, CH), 109.1 (Ar, CH), 106.8 (Ar, CH), 47.2 (CH), 28.0 (CH_2), 12.4 ppm (Me); IR ($CHCl_3$, cm^{-1}): $\tilde{\nu}=$2930, 1690, 1432, 1356, 740, 696 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{20}O_2$ $[M]^+$: 328.1463; found: 328.1458.

3-Phenyl-5-(1-phenylpropyl)-2-(thiophen-2-yl)furan 2c: From 48 mg (0.14 mmol) of 2,3,4-trien-1-ol **1c**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as the eluent, compound **2c** (29 mg, 61%, method A; 20 mg, 42%, method B) was produced as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=7.39$ (dd, 2H, $J=8.3$, 1.6 Hz, Ar), 7.28 (m, 7H, Ar), 7.20 (m, 1H, Ar), 7.09 (dd, 1H, $J=5.1$, 1.0 Hz, Ar), 7.06 (dd, 1H, $J=3.7$, 1.0 Hz, Ar), 6.87 (dd, 1H, $J=5.0$, 3.7 Hz, Ar), 6.09 (s, 1H, Ar), 3.81 (t, 1H, $J=$ 7.6 Hz, CH), 2.15 (m, 1H, $J=7.3$ Hz, C*H*H), 1.92 (m, 1H, $J=7.4$ Hz, CH*H*), 0.90 ppm (t, 3H, $J=7.3$ Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=157.2$, 142.9, 142.2, 133.9, 133.5, 128.7 (Ar, 4CH), 128.5 (Ar, 2CH), 128.0 (Ar, 2CH), 127.3 (Ar, CH), 127.1 (Ar, CH), 126.6 (Ar, CH), 124.2 (Ar, CH), 123.6 (Ar, CH), 122.6, 109.7 (Ar, CH), 47.2 (CH), 28.0 (CH_2), 12.4 ppm (Me); IR ($CHCl_3$): νÜ=>=2945, 1587, 1349, 753, 699 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{20}OS$ $[M]^+$: 344.1235; found: 344.1236.

1-Methyl-2-[3-phenyl-5-(1-phenylpropyl)furan-2-yl]-1*H*-indole 5a: From 31 mg (0.08 mmol) of 2,3,4-trien-1-ol **4a**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as the eluent, compound **5a** (19 mg, 62%, method A; 22 mg, 71%, method B) was produced as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=7.52$ (d, 1H, $J=7.7$ Hz, Ar), 7.28 (m, 6H, Ar), 7.18 (m, 6H, Ar), 7.05 (t, 1H, $J=7.3$ Hz, Ar), 6.56 (s, 1H, Ar), 6.34 (s, 1H, Ar), 3.85 (t, 1H, $J=7.7$ Hz, CH), 3.44 (s, 3H, NMe), 2.17 (m, 1H, $J=$ 7.3 Hz, C*H*H), 1.95 (m, 1H, $J=7.6$ Hz, CH*H*), 0.92 ppm (t, 3H, $J=$ 7.3 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=158.7$, 147.2, 140.2, 137.8, 133.4, 130.9, 128.5 (Ar, 2CH), 128.4 (Ar, 2CH), 128.0, 127.7 (Ar, 2CH), 127.5 (Ar, 2CH), 126.9 (Ar, CH), 126.7 (Ar, CH), 125.7, 122.1 (Ar, CH), 120.9 (Ar, CH), 119.7 (Ar, CH), 109.5 (Ar, CH), 107.8

(Ar, CH), 103.5 (Ar, CH), 47.4 (CH), 31.0 (NMe), 27.7 (CH_2), 12.4 ppm (Me); IR ($CHCl_3$): $\tilde{\nu}$ = 2924, 1764, 1676, 1457, 753, 700 cm^{-1}; HRMS (ES): calcd for $C_{28}H_{25}NO$ $[M]^+$: 391.1936; found: 391.1935.

General procedure for the Pd^{II}-catalyzed heterocyclization/cross-coupling of 2,3,4-trien-1-ols 1 and 4 with bromoprop-1-enes

Preparation of tetrasubstituted furans 3 and 6

Palladium(II) chloride (0.05 mmol) was added to a stirred solution of the appropriate 2,3,4-trien-1-ol **1** or **4** (1.0 mmol) and the corresponding bromoprop-1-ene derivative (3.0 mmol) in *N*,*N*-dimethylformamide (6.0 mL). The reaction was stirred under an argon atmosphere at the appropriate temperature (RT or −10 °C) until disappearance of the starting material was observed (TLC, typically 12 h). Water (3.0 mL) was added before being extracted with ethyl acetate (3×10 mL). The organic phase was washed with water (2× 4 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure adducts **3** and **6**.

3-(2-Methylallyl)-4,5-diphenyl-2-(1-phenylpropyl)furan 3ab: From 53 mg (0.16 mmol) of 2,3,4-trien-1-ol **1a**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as the eluent, compound **3ab** (35 mg, 57%) was produced as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.32 (m, 4H, Ar), 7.24 (m, 4H, Ar), 7.13 (m, 7H, Ar), 4.60 (dd, 1H, *J* = 1.9, 1.3 Hz, =C*H*H), 4.43 (d, 1H, *J* = 1.0 Hz, =CH*H*), 3.80 (t, 1H, *J* = 7.7 Hz, CH), 2.83 (s, 2H, CH_2), 2.17 (m, 1H, *J* = 7.9 Hz, C*H*H), 2.01 (m, 1H, *J* = 7.3 Hz, CH*H*), 1.59 (s, 3H, Me), 0.86 ppm (t, 3H, *J* = 7.3 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 152.3, 146.4, 144.0, 143.1, 134.2 131.5, 130.1 (Ar, 2CH), 128.5 (Ar, 2CH), 128.3 (Ar, 2CH), 128.2 (Ar, 2CH), 128.0 (Ar, 2CH), 127.1 (Ar, CH), 126.5 (Ar, CH), 126.3 (Ar, CH), 125.0 (Ar, 2CH), 124.2, 119.3, 111.3 (=CH_2), 45.3 (CH), 31.3 (CH_2), 28.4 (CH_2), 22.6 (Me), 12.8 ppm (Me); IR ($CHCl_3$): $\tilde{\nu}$ = 2943, 1789, 1654, 1432, 757, 710 cm^{-1}; HRMS (ES): calcd for $C_{29}H_{28}O$ $[M]^+$: 392.2140; found: 392.2133.

4-Allyl-3-phenyl-5-(1-phenylpropyl)-2,2′-bifuran 3ba: From 50 mg (0.15 mmol) of 2,3,4-trien-1-ol **1b**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as the eluent, compound **3ba** (36 mg, 65%) was produced as a colorless oil. ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.43 (d, 2H, *J* = 7.2 Hz, Ar), 7.28 (d, 2H, *J* = 8.2 Hz, Ar), 7.11 (m, 6H, Ar), 6.95 (d, 1H, *J* = 1.8 Hz, Ar), 6.28 (d, 1H, *J* = 3.4 Hz, Ar), 5.98 (dd, 1H, *J* = 1.8, 3.4 Hz, Ar), 5.66 (m, 1H, =CH), 4.85 (m, 2H, =CH_2), 3.86 (t, 1H, *J* = 7.2 Hz, CH), 2.99 (dd, 2H, *J* = 5.7, 1.3 Hz, CH_2), 2.34 (m, 1H, *J* = 7.3 Hz, C*H*H), 2.07 (m, 1H, *J* = 7.2 Hz, CH*H*), 0.91 ppm (t, 3H, *J* = 7.3 Hz, Me); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 153.0, 141.2, 143.4, 141.7 (Ar, CH), 136.8 (=CH), 133.5, 130.5, (Ar, 2CH), 128.9 (Ar, 2CH), 127.6 (Ar, 4CH), 126.8 (Ar, 2CH), 119.2, 115.4 (=CH_2), 111.3 (Ar, CH), 106.3 (Ar, CH), 45.9(CH), 28.5 (CH_2), 27.7 (CH_2), 12.9 ppm (Me); IR ($CHCl_3$): $\tilde{\nu}$ = 2926, 1767, 1670, 1452, 760, 701 cm^{-1}; HRMS (ES): calcd for $C_{26}H_{24}O_2$ $[M]^+$: 368.1776; found: 368.1788.

4-(2-Bromoallyl)-3-phenyl-5-(1-phenylpropyl)-2,2′-bifuran 3bc: From 29 mg (0.09 mmol) of 2,3,4-trien-1-ol **1b**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as the eluent, compound **3bc** (24 mg, 59%) was produced as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.32 (m, 11H, Ar), 6.34 (dd, 1H, *J* = 3.4, 1.7 Hz, Ar), 6.24 (dd, 1H, *J* = 3.4, 0.7 Hz, Ar), 5.35 (d, 1H, *J* = 1.7 Hz, =C*H*H), 5.30 (d, 1H, *J* = 1.7 Hz, =CH*H*), 3.88 (t, 1H, *J* = 7.7 Hz, CH), 3.40 (s, 2H, CH_2), 2.24 (m, 1H, *J* = 7.3 Hz, C*H*H), 2.09 (m, 1H, *J* = 7.3 Hz, CH*H*), 0.95 ppm (t, 3H, *J* = 7.3 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 153.5, 146.4, 144.4, 143.6, 141.5 (Ar, CH), 140.4, 131.5, 129.8 (Ar, 2CH), 128.4 (Ar, 2CH), 128.3 (Ar, 2CH), 128.0 (Ar, 2CH), 127.5 (Ar, CH), 126.5 (Ar, CH), 126.4, 117.5 (=CH_2), 117.2, 111.0 (Ar, CH), 106.0 (Ar, CH), 45.5 (CH), 35.6 (CH_2), 28.1 (CH_2), 12.7 ppm (Me); IR ($CHCl_3$): $\tilde{\nu}$ = 2945, 1754, 1643, 1432, 756, 697 cm^{-1}; HRMS (ES): calcd for $C_{26}H_{23}O_2Br$ $[M]^+$: 446.0881; found: 446.0880.

3-(2-Bromoallyl)-4-phenyl-2-(1-phenylpropyl)-5-(thiophen-2-yl)-furan 3cc: From 50 mg (0.14 mmol) of 2,3,4-trien-1-ol **1c**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as the eluent, compound **3cc** (38 mg, 61%) was produced as a colorless oil. ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.37 (d, 2H, *J* = 7.2 Hz, Ar), 7.11 (m, 9H, Ar), 6.66 (dd, 1H, *J* = 5.0, 1.0 Hz, Ar), 6.58 (d, 1H, *J* = 5.1, 3.7 Hz, Ar), 5.18 (d, 1H, *J* = 1.5 Hz, =C*H*H), 5.07 (d, 1H, *J* = 1.7 Hz, =CH*H*), 3.79 (t, 1H, *J* = 7.7 Hz, CH), 3.30 (m, 2H, CH_2), 2.28 (m, 1H, *J* = 7.6 Hz, C*H*H), 2.04 (m, 1H, *J* = 7.3 Hz, CH*H*), 0.88 ppm (t, 3H, *J* = 7.3 Hz, Me); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 153.4, 144.3, 142.8, 134.0, 133.0, 131.9, 130.5 (Ar, 2CH), 128.9 (Ar, 4CH), 127.4 (Ar, 2CH), 126.9 (Ar, CH), 125.2 (Ar, 2CH), 124.1 (Ar, CH), 123.3 (Ar, CH), 118.2, 117.8 (=CH_2), 45.9 (CH), 36.0 (CH_2), 28.6 (CH_2), 12.9 ppm (Me); IR ($CHCl_3$): $\tilde{\nu}$ = 2920, 1754, 1672, 1434, 780, 700 cm^{-1}; HRMS (ES): calcd for $C_{26}H_{23}OSBr$ $[M]^+$: 462.0653; found: 462.0669.

Trimethyl[4-(2-methylallyl)-2-phenyl-5-propylfuran-3-yl]silane 3eb: From 49 mg (0.15 mmol) of 2,3,4-trien-1-ol **1e**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as the eluent, compound **3eb** (35 mg, 74%) was produced as a colorless oil. ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.75 (dd, 2H, *J* = 8.5, 1.5 Hz, Ar), 7.10 (m, 3H, Ar), 5.88 (m, 1H, =CH), 4.86 (m, 2H, =CH_2), 3.11 (s, 2H, CH_2), 2.50 (m, 2H, CH_2), 1.65 (s, 3H, Me), 1.62 (m, 2H, CH_2), 0.87 (t, 3H, *J* = 7.3 Hz, Me), 0.27 ppm (s, 9H, $SiMe_3$); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 153.0, 145.0, 134.3, 128.9 (Ar, 2CH), 126.9 (Ar, CH), 123.7 (Ar, 2CH), 122.2, 119.3, 111.7 (=CH_2), 108.1, 30.2 (CH_2), 28.2 (CH_2), 23.3 (CH_2), 23.2 (Me), 14.1 (Me), 1.1 ppm ($SiMe_3$); IR ($CHCl_3$): $\tilde{\nu}$ = 2930, 1734, 1654, 1421, 745, 695 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{28}OSi$ $[M]^+$: 312.1909; found: 312.1906.

2-[4-(2-Bromoallyl)-3-phenyl-5-(1-phenylpropyl)furan-2-yl]-1-methyl-1*H*-indole 6ac: From 75 mg (0.19 mmol) of indole-tethered 2,3,4-trien-1-ol **4a**, and after chromatography of the residue using hexanes/ethyl acetate (10:1) as the eluent, compound **6ac** (45 mg, 46%) was produced as a colorless oil. ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.59 (d, 1H, *J* = 7.9 Hz, Ar), 7.45 (d, 2H, *J* = 7.2 Hz, Ar), 7.32 (m, 3H, Ar), 7.16 (m, 8H, Ar), 6.75 (d, 1H, *J* = 0.7 Hz, Ar), 5.39 (d, 1H, *J* = 1.6 Hz, =C*H*H), 5.33 (d, 1H, *J* = 1.7 Hz, =CH*H*), 3.96 (t, 1H, *J* = 7.9 Hz, CH), 3.35 (s, 3H, NMe), 3.32 (m, 2H, CH_2), 2.36 (m, 1H, *J* = 7.2 Hz, C*H*H), 2.15 (m, 1H, *J* = 7.0 Hz, CH*H*), 1.00 ppm (t, 3H, *J* = 7.3 Hz, Me); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 154.8, 142.7, 142.2, 138.4, 133.3, 132.1, 130.6, 129.8 (Ar, 2CH), 129.3 (Ar, 2CH), 128.7 (Ar, 2CH), 128.6 (Ar, 2CH), 128.1 (Ar, CH), 127.0 (Ar, CH), 126.5 (2C), 122.5 (Ar, CH), 121.3 (Ar, CH), 120.4 (Ar, CH), 117.9 (=CH_2), 117.3, 109.8 (Ar, CH), 103.9 (Ar, CH), 45.8 (CH), 34.9 (CH_2), 31.2 (NMe), 28.0 (CH_2), 12.8 ppm (Me); IR ($CHCl_3$): $\tilde{\nu}$ = 2932, 1709, 1623, 1356, 746, 699 cm^{-1}; HRMS (ES): calcd for $C_{31}H_{28}BrNO$ $[M]^+$: 509.1354; found: 509.1351.

2-[4-Allyl-3-phenyl-5-(1-phenylpropyl)furan-2-yl]-3-iodo-1-methyl-1*H*-indole 6ba: From 47 mg (0.09 mmol) of indole-tethered 2,3,4-trien-1-ol **4b**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as the eluent, compound **6ba**

(21 mg, 42%) was produced as a colorless oil. ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.76 (m, 1H, Ar), 7.46 (d, 2H, J = 7.4 Hz, Ar), 7.16 (m, 7H, Ar), 6.94 (m, 3H, Ar), 6.79 (m, 1H, Ar), 5.83 (m, 1H, =CH), 4.98 (m, 2H, =CH_2), 3.91 (t, 1H, J = 7.0 Hz, CH), 3.17 (d, 2H, J = 5.4 Hz, CH_2), 2.79 (d, 3H, J = 6.5 Hz, NMe), 2.36 (m, 1H, J = 7.3 Hz, C*H*H), 2.08 (m, 1H, J = 7.1 Hz, CH*H*), 0.96 ppm (q, 3H, J = 7.5 Hz, Me); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 155.7, 143.3, 138.5, 137.2, 137.1 (=CH), 133.3, 131.1, 130.1, 129.7 (Ar, 2CH), 129.3 (Ar, 2CH), 129.2 (Ar, 2CH), 128.7 (Ar, 2CH), 127.8 (Ar, CH), 126.9 (Ar, CH), 123.6 (Ar, CH), 121.1, 121.0 (Ar, CH), 120.0 (Ar, CH), 117.8, 116.7, 115.8 (=CH_2), 110.2 (Ar, CH), 46.0 (CH), 30.8 (NMe), 28.7 (CH_2), 28.0 (CH_2), 13.0 ppm (Me); IR ($CHCl_3$): $\tilde{\nu}$ = 2925, 1712, 1611, 1364, 752, 702 cm^{-1}; HRMS (ES): calcd for $C_{31}H_{28}NOI$ $[M]^+$: 557.1216; found: 557.1197.

3-Iodo-1-methyl-2-[4-(2-methylallyl)-3-phenyl-5-(1-phenylpropyl)furan-2-yl]-1*H*-indole 6bb: From 80 mg (0.16 mmol) of indole-tethered 2,3,4-trien-1-ol **4b**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as the eluent, compound **6bb** (56 mg, 61%) was produced as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.80 (m, 1H, Ar), 7.61 (d, 2H, J = 7.1 Hz, Ar), 7.30 (m, 7H, Ar), 7.06 (m, 3H, Ar), 6.92 (m, 1H, Ar), 5.00 (s, 1H, =C*H*H), 4.95 (s, 1H, =CH*H*), 4.06 (t, 1H, J = 7.3 Hz, CH), 3.18 (s, 2H, CH_2), 2.95 (s, 3H, NMe), 2.50 (m, 1H, J = 7.2 Hz, C*H*H), 2.23 (m, 1H, J = 7.0 Hz, CH*H*), 1.74 (s, 3H, Me), 1.10 ppm (t, 3H, J = 7.4 Hz, Me); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 154.1, 147.9, 146.1, 144.2, 138.5, 134.0, 131.0, 129.8 (Ar, 2CH), 129.4, 129.2 (Ar, 2CH), 129.1 (Ar, 2CH), 129.0 (Ar, CH), 127.5 (Ar, CH), 127.1 (Ar, CH), 122.4 121.3 (Ar, CH), 120.3 (Ar, CH), 118.7 (Ar, CH), 111.9 (=CH_2), 109.8 (Ar, CH), 103.8 (Ar, CH), 45.8 (CH), 31.9 (CH_2), 31.1 (NMe), 28.6 (CH_2), 13.0 ppm (Me); IR ($CHCl_3$): $\tilde{\nu}$ = 2918, 1728, 1623, 1369, 749, 697 cm^{-1}; HRMS (ES): calcd for $C_{32}H_{30}NOI$ $[M]^+$: 571.1372; found: 571.1349.

General procedure for the Pd^{II}-catalyzed carbocyclization/cross-coupling of protected 2,3,4-trien-1-ol 8 with bromoprop-1-enes

Preparation of trisubstituted carbazoles 7

Palladium(II) chloride (0.005 mmol) was added to a stirred solution of the protected 2,3,4-trien-1-ol **8** (0.10 mmol) and the corresponding bromoprop-1-ene derivative (0.30 mmol) in *N*,*N*-dimethylformamide (0.6 mL). The reaction was stirred under argon atmosphere at room temperature until disappearance of the starting material (TLC, 12 h). Water (0.5 mL) was added before being extracted with ethyl acetate (3×3 mL). The organic phase was washed with water (2×1 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure adducts **7**.

(*E*)-9-Methyl-3-(2-methylallyl)-2-phenyl-4-(1-phenylprop-1-enyl)-9*H*-carbazole 7ab: From 54 mg (0.11 mmol) of protected 2,3,4-trien-1-ol **8**, and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent gave compound **7ab** (15 mg, 31%) as a colorless oil; ^{1}H NMR (300 MHz, [D$_6$]acetone, 25 °C): δ = 8.05 (d, 1H, J = 7.9 Hz, Ar), 7.55 (d, 1H, J = 8.2 Hz, Ar), 7.38 (m, 9H, Ar), 7.24 (t, 1H, J = 7.4 Hz, Ar), 7.19 (t, 1H, J = 7.4 Hz, Ar), 7.03 (t, 1H, J = 7.6 Hz, Ar), 6.60 (q, 1H, J = 6.8 Hz, =CH), 4.48 (s, 1H, =C*H*H), 4.13 (s, 1H, =CH*H*), 3.97 (s, 3H, NMe), 3.20 (q, 2H, J = 12.9 Hz, CH_2), 1.52 (d, 3H, J = 7.0 Hz, Me), 1.38 ppm (s, 3H, Me); ^{13}C NMR (75 MHz, [D$_6$]acetone, 25 °C): δ = 146.0, 144.3, 142.7, 142.1, 140.6, 140.5, 135.0, 130.3 (Ar, 2CH), 129.2 (Ar, 2CH), 128.6 (Ar, 2CH), 127.6 (Ar, CH), 127.5 (Ar, CH), 127.3, 126.8 (Ar, 2CH), 126.4 (Ar, CH), 126.4 (=CH), 123.4, 122.4 (Ar, CH), 121.3, 119.7 (Ar, CH), 111.5 (=CH_2), 110.4 (Ar, CH), 109.4 (Ar, CH), 38.2 (CH_2), 30.1 (NMe), 16.1 ppm (Me); IR ($CHCl_3$): $\tilde{\nu}$ = 2930, 1464, 1313, 1180, 787, 661 cm^{-1}; HRMS (ES): calcd for $C_{32}H_{29}N$ $[M]^+$: 427.2300; found: 427.2313.

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